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Editorial

Pseudoangina

George L. Engel, M.D., Rochester, N. Y.*

A common and vexing problem for the cardiologist—as well as for physicians in general—is the patient who presents with a syndrome of chest pain suggesting angina pectoris but whose physical and laboratory examinations fail to provide unequivocal supporting evidence for the presence of coronary artery disease. Among some of these patients the clinical history is so clear-cut and conforms so perfectly to the criteria for angina pectoris that one makes the diagnosis with confidence in spite of the absence of other evidence, and it is usually confirmed within a short time by the development of the more definitive diagnostic signs. Other patients, however, present histories which deviate in subtle or confusing details from classic angina pectoris, provoking doubts among even the most seasoned and confident cardiologists. This is especially so when there are also equivocal electrocardiographic findings. The potentially serious nature of the disease is so great that in diagnosis one tends to err in commission rather than in omission. Yet in every physician's practice are patients suspected of having coronary artery disease who go on with repeated symptoms, month after month, year after year, without any more definitive diagnosis possible. In spite of the doctor's best intentions, the patient becomes a cardiac cripple. The physician maintains his strong suspicion that this is not coronary artery disease, yet is continually plagued with doubt that it might be.

Why does this dilemma exist? Because, I believe, of insufficient understanding of what the condition is if it isn't angina pectoris. While a number of dubious and not too convincing mechanisms have been invoked, such as muscle spasm, costochondritis, hypoglycemia, etc., convincing evidence has not been presented that such mechanisms pertain in more than a few cases. On the other hand, most

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*Professor of Psychiatry and Associate Professor of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, N.Y.

physicians vaguely or strongly suspect that psychological or emotional mechanisms are involved in some way or other in the genesis of the pain of these patients. Careful study of many such patients satisfies me that this suspicion is well grounded. Furthermore, clear-cut criteria exist which permit one not only to identify with accuracy the pain of such origin, but also to differentiate and evaluate this type of pain syndrome from true angina pectoris. It is the unfamiliarity with the criteria necessary to establish positively (rather than by exclusion) that the pain is of psychological origin which makes it so difficult for the physician to settle for himself that the patient does not have coronary artery disease—and if the patient does have coronary disease, to evaluate the degree to, and frequency with, which the attacks of pain can be explained on the basis of the coronary disease.

Elsewhere I have described in detail the criteria necessary to diagnose psychogenic pain and to identify the pain-prone patient.[1] I will summarize here only the salient diagnostic points. The reader is referred to the original paper for a clarification of the concept of "psychogenic pain." Suffice it to say that pain may constitute a purely psychic phenomenon and yet may be experienced by the patient as located in some discrete anatomic site, e.g., substernally or precordially, not differing for the patient from pain that originates in local disease process. Study reveals that such pain experiences are more likely to occur in individuals whose development and background predispose them to the use of pain as a part of psychic adjustment, and that there are identifiable reasons why the pain is experienced where it is in the body schema and why it develops when it does. I have designated these persons as "pain-prone," meaning that they are more prone to experience pain as a psychic regulating process, regardless of whether it originates from a peripheral pathologic process or develops as a purely psychic process.

When such individuals suffer from chest pain, the syndrome so often simulates coronary disease as to present the diagnostic dilemma already described. The following provides a guide for the correct identification of this type of patient and the differentiation of this pain syndrome from true angina pectoris. It must be emphasized that the application of an interview technique which permits the patient to formulate his illness in his own terms and to speak freely of family and personal life is essential if the requisite information is to be obtained. This does not mean a lengthy "psychiatric" history but does require that the physician listen attentively for this kind of data, and avoid an approach which tends to suggest to these very suggestible patients the symptoms which the physician wants to hear about. This may require a more lengthy initial interview, but in the long run it is enormously economical of time.

1. The pain and associated manifestations differ from true angina pectoris in subtle respects as to quality, timing, radiation, provoking and alleviating factors, etc. It is this feature which usually raises the doubts of the physician. However, it must be emphasized that some of these patients, after having been subjected to pointed and directive interview experiences, may present histories indistinguishable from true angina. The same may be true of the patient whose pain episodes were actually preceded by a myocardial infarction, or of patients

who have an intimate knowledge of angina through close contact with a patient or through familiarity, as is occasionally the case when a physician or nurse is the patient.

2. In the history of the pain-prone patient, one usually finds multiple previous painful illnesses and injuries. One should not be misled by the fact that some patients may report these as attacks of "kidney colic," "gall bladder attacks," "pleurisy," "a disc," etc., and that indeed some (but usually not all) may actually have experienced such illnesses. The diagnostic clue is the multiplicity and frequency of the pain episodes and the degree of suffering described by the patient, often out of proportion to what might reasonably be expected, even for such traditionally painful illnesses. More often the pain is not understandable in such terms and represents another episode of psychogenic pain. Especially among women, a history in adolescence of "appendicitis" which does not conform to the usual story of acute appendicitis is of diagnostic value.

3. In keeping with the foregoing, one is apt to discover an unusually high incidence of previous surgical operations or painful treatments. While some of these procedures may have been indicated, in others one is often left with the impression that they were solicited by the patient in such a way that the physician found it difficult not to comply.

4. The past life history of these individuals is often marked by a prominence of unpleasant and disagreeable experiences and relationships. They seem to have been beset by bad luck or to be the victims of harsh fate, but more careful scrutiny usually reveals that such hardships or defeats often could have been avoided, if they were not actually solicited. Indeed, one discovers these people to be intolerant of success or good fortune, often enjoying the best health when the going is toughest, and falling ill when fortune smiles. The paradox is that the painful disability may develop at a time when external pressures are relieved or a success is achieved—the opposite of what one might reasonably expect. As is shown elsewhere, such behavior is indicative of powerful unconscious feelings of guilt, and pain is utilized by these people as a means of atonement. Technically, these are masochistic characters for whom pain, punishment, suffering, and defeat form important devices whereby guilt is appeased and human relationships sustained.

5. The location of the patient's pain may correspond to the site of (a) a pain experienced by some person important to the patient (who may actually have suffered a coronary occlusion); (b) a pain which the patient imagined or unconsciously wished another person had experienced; (c) a past pain of the patient's which originated from a peripheral organic process, often a previous coronary occlusion, and which occurred in a setting in which the pain and illness served for the patient the psychological functions already noted. In the last case the patient may thereafter re-experience similar or identical pain without further coronary disease. In the first two instances the psychological mechanism involved is identification. Since this is an unconscious process it is rarely productive to ask a patient directly "Does anyone else have pain like yours?" Much more effective is the more casual elicitation of the family illness record in which the patient is simply asked about the health and symptoms of each of the im-

portant family members (or others), without any obvious attempt to link them with the patient's illness. A common and diagnostically helpful sign is that the patient may indicate the site of his own pain while describing the other person's symptom.

6. The episode or episodes of pain may occur in settings in which the patient is threatened with or has suffered the loss of an important relationship, valued object or function, or when he experiences unacceptable anger toward a love object. The pain may occur during or in place of a period of grief.

It is usually not difficult to obtain from the patient the information necessary to satisfy such criteria, especially if the physician is alert to its importance and follows an interview technique which permits the patient to reveal such data. Some of these patients have a sufficiently pronounced need to exhibit their suffering, and with only a little encouragement the doctor may literally be inundated with a tale of woe of striking proportions. Yet he may note that the patient tells the story with a certain amount of relish and may complain of intense pain with a bland expression, even a smile.

When the physician is in possession of such information, the recognition of the patient as "pain-prone" is relatively certain, and it is usually not difficult to settle that the pain experience itself is primarily psychological and not an expression of coronary artery disease. Yet, obviously, a certain proportion of the pain-prone patients also have or will develop coronary disease. How, in these patients, can a coronary attack be distinguished from the other pain so that the physician knows when the appropriate laboratory tests should be repeated? The most consistently reliable finding is that the new coronary episode is different both as described as well as experienced by the patient, a fact which the patient often volunteers, if only in terms of its being "worse." Careful inquiry often reveals other changes from the pain pattern which existed up to then. Paradoxically, some patients may minimize the true attack, and others may propose a psychological origin even though they vigorously resisted any such interpretation of the other attacks.

The physician who is well acquainted with this syndrome and understands the psychology underlying it will continue to make diagnostic errors, but they will be fewer and less serious than those made by his colleague who is not so informed.

REFERENCE

1. Engel, G. L.: Psychogenic Pain and the Pain-Prone Patient, Am. J. Med. **26**:899, 1959.

Clinical Communications

Vectorcardiographic and Electrocardiographic Changes Following Surgical Correction of Atrial Septal Defect

Jonas Beregovich, M.D., Selvyn Bleifer, M.D., Ephraim Donoso, M.D., and Arthur Grishman, M.D., New York, N. Y.*

INTRODUCTION

Atrial septal defect of the secundum type is one of the most common congenital intracardiac lesions amenable to surgical repair. It would be desirable to have a simple method of determining the adequacy of closure of the defect. One would expect, for example, that there would be a regression in the pattern of right ventricular hypertrophy on the electrocardiogram. This has been shown to be true by several authors.[1-4] The vectorcardiogram is another objective measure in regard to the diagnosis of right ventricular hypertrophy, and for this reason it has been decided to study the vectorcardiographic modifications postoperatively. These vectorcardiographic changes as well as indicating the success of surgery may also provide information about the genesis of the pattern of right ventricular hypertrophy. This report describes the changes in the ECG and VCG in 12 cases of atrial septal defect of the secundum type, with follow-up of from 2 to 12 months after surgery.

METHODS AND MATERIAL

Twelve patients with proved atrial septal defect of the secundum type form the basis of this report (Table I). Twelve-lead electrocardiograms and vectorcardiograms were taken preoperatively and every 2 months postoperatively. For vectorcardiograms, the cube method of electrode placement was used.[5]

The criteria for the electrocardiographic diagnosis of right ventricular hypertrophy were those established by Milnor.[6] The vectorcardiographic criteria for the diagnosis of right ventricular hypertrophy were those previously described from this laboratory.[5]

All patients had preoperative right heart catheterization demonstrating a significant oxygen step-up in the right atrium. Open-heart surgery utilizing a pump-oxygenator bypass was used in all cases.

From the Division of Cardiology, Departments of Medicine and Pediatrics, The Mount Sinai Hospital, New York, N. Y.

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*Fellow of John Simon Guggenheim Memorial Foundation.

In 2 cases (Cases 11 and 12) a significant systolic pressure gradient across the pulmonary valve, signifying pulmonary obstruction, was found preoperatively. However, the clinical picture, the rest of the hemodynamic studies, and the findings at operation indicated the atrial septal defect to be the predominant lesion.

One patient (Case 8) was recatheterized 8 months after surgery. Pressure values and gasometric and dye dilution studies were normal.

TABLE I

CASE	AGE (YR.)	R.V. PRESSURE (MM. Hg)	P.A. PRESSURE (MM. Hg)	R.A. OXYGEN STEP-UP (VOL. %)	V_1 PATTERN
1. M.B.	8	27/5	24/8	2.0	rsR′
2. R.E.	17	34/7	25/8	2.5	rSR′
3. M.I.	14	30/7	24/9	3.0	rSR′
4. J.K.	16	18/2	18/11.5	2.0	rSr′
5. R.L.	19	30/6	28/11	4.0	rSR′
6. C.M.	9	33/6	30/8	1.7	rsR′
7. C.R.	12	37/4	24/8	3.0	rSr′
8. B.R.	11	45/9	24/10	2.1	rS
9. J.B.	6	41/3	32/7	3.6	rsR′
10. A.M.	14	30/2	20/11	3.0	Rs
11. E.I.	13	69/7	16/10	2.0	rSR′S′
12. L.W.	13	80/10	31/10	4.0	R

RESULTS

Electrocardiogram.—The electrocardiographic findings prior to operation were fairly constant. The ventricular complex can be summarized as follows (Table II): (1) The majority of patients showed right axis deviation, the electrical axis being between plus 90 and plus 150 degrees. In 1 case there was an electrical axis of minus 150 degrees and a concordant S pattern in the electrocardiogram. (2) The predominant QRS pattern in Lead V_1 was an RSR′ which was present in 9 cases. In 3 others (Cases 8, 10, and 12) there were rS, Rs, and an R pattern observed. No consistent correlation was found between the various QRS patterns observed in Lead V_1 and the hemodynamic findings. (3) The R/S or R′/S ratio in Lead V_1 was generally greater than 1 (9 cases), and the R/S ratio in Lead V_6 reflected the presence of a deep S wave. (4) The QRS interval was found to be within 0.07 to 0.10 second, except for Case 10, in which it measured 0.13 second.

According to the electrocardiographic criteria of Milnor,[6] a diagnosis of right ventricular hypertrophy could be made in 9 cases. In the other 3 cases (Cases 4, 5, and 7) with an rSr′ pattern in Lead V_1 and an R/S or R′/S ratio of less than 1 in Lead V_1, or an R or R′ less than 0.5 millivolts, the electrocardiogram would not fit the above-mentioned criteria. However, when conventional electrocardiographic criteria were applied, a diagnosis of incomplete right bundle branch block was suggested.

Following repair of the septal defect and in the period of observation (from 2 to 12 months) the changes listed below were evident.

1. There was normalization or diminution of the right axis deviation. The

difference, measured in degrees comparing the preoperative electrocardiogram and the last postoperative control, varied between a maximum of 60 (Case 11, Fig. 1) and a minimum of 5 degrees (Case 12).

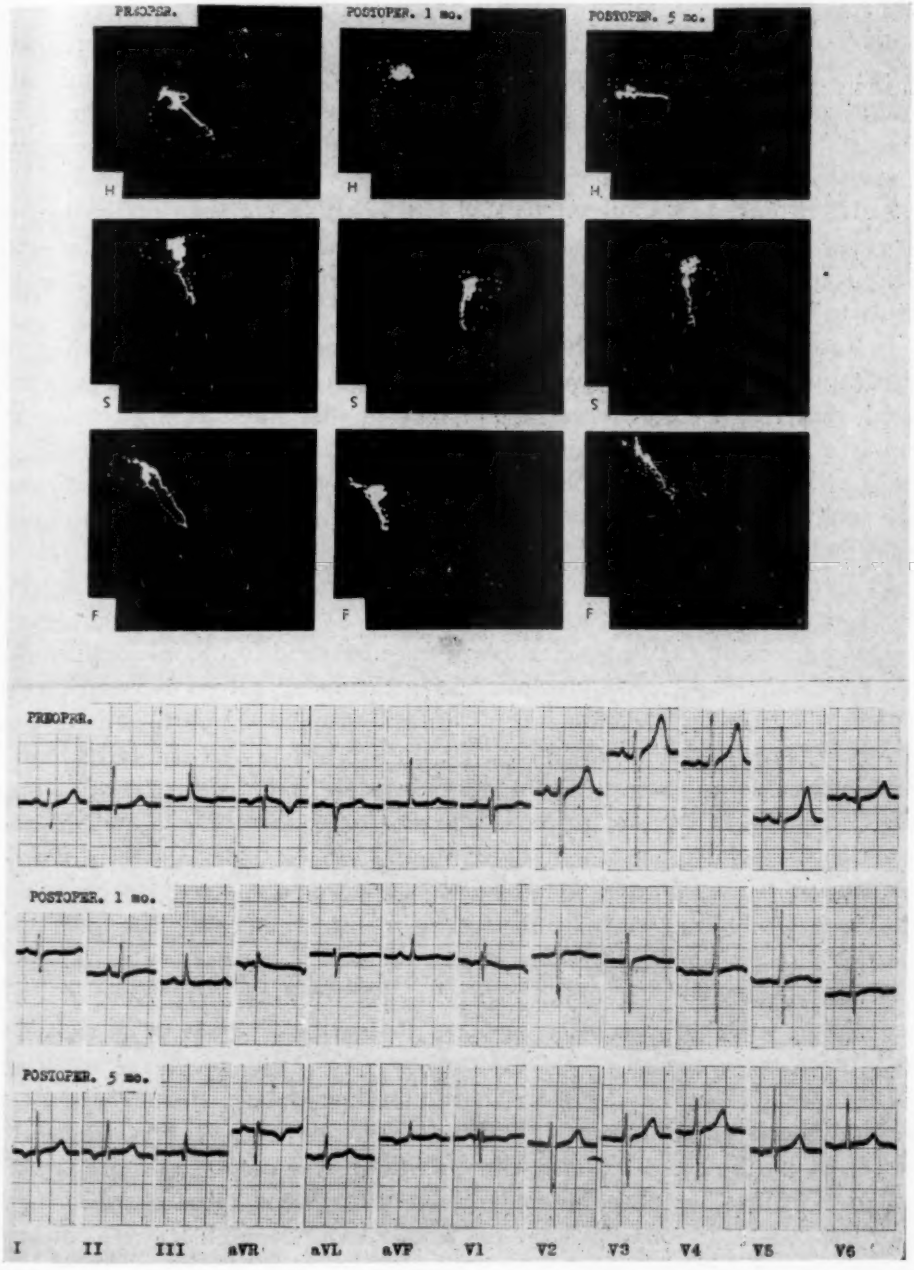

Fig. 1.—Case 11, E.I. There is a complete normalization of the vectorcardiogram 5 months following surgical correction of an atrial septal defect. In the ECG the axis deviation becomes normal and the R′ in V_1 decreases in amplitude, but the RSR′ pattern persists. The sense of rotation of the QRS loop is indicated by the blunt end of the comma-shaped interrupted dots which point in the direction that the loop is traversing.

2. The RSR′ pattern in Lead V_1 persisted in almost all of the cases in which it was present prior to surgery. Only in 1 case (Case 1) was a preoperative RSR′ pattern replaced by an RS pattern postoperatively (Fig. 2). In another case, a preoperative R pattern in Lead V_1 changed to an RSR′ pattern postoperatively (Case 12, Fig. 3).

3. A clear diminution in the amplitude of the R or R′ with inversion of the R/S ratio in Lead V_1, a greater amplitude of the R wave, and diminution of the depth of the S wave in the left precordial leads were observed (Figs. 3 and 4).

4. In 5 cases the QRS interval diminished after surgery, and in the remainder was unchanged.

Little attention was given to S-T and T-wave changes in the immediate postoperative period. In many cases the changes may not reflect the status of the myocardium, but may be due to a pericarditis and, therefore, would be difficult to interpret.

In summary, all of the cases showed a tendency to postoperative electrocardiographic restoration toward normal; that is, when the same criteria were applied, right ventricular hypertrophy could be diagnosed in only 2 cases (Cases 9 and 12). In 5 cases the electrocardiogram was neither normal nor diagnostic of right ventricular hypertrophy; these cases are considered as "nondiagnostic" in the tables. In 5 other cases the electrocardiogram was considered to be within normal limits.

Vectorcardiogram (*Table III*).—The vectorcardiographic findings prior to operation were similar to those described by Silverblatt and associates.[7] The principal pattern in the horizontal plane is an anteriorly placed loop, sometimes displaced to the right, and clockwise in rotation or a figure-of-eight (Fig. 5). In the sagittal plane, the QRS loop is anterior to the E point, and the sense of rotation is usually counterclockwise. In the frontal plane, the QRS loop is inscribed clockwise and sometimes displaced to the right. The T loop is opposite to the QRS loop. In 9 cases the VCG was similar to the above-described pattern. In 1 case (Case 9), there was a right bundle branch block pattern, and in the other 2 cases (Cases 10 and 12) the QRS loop was displaced more to the right in the horizontal plane, and the electrocardiogram showed an Rs and R pattern in Lead V_1, respectively (Figs. 3 and 6).

The preoperative vectorcardiographic conclusions were right ventricular hypertrophy, with the exception of Case 9, in which a pattern of right bundle branch block was present.

Postoperatively, the vectorcardiograms taken in sequence showed a gradual transition toward less abnormal, or a complete normalization of, the QRS and T loops. In the horizontal plane, the QRS loop was displaced more toward the left. The terminal limb became progressively displaced more posteriorly, giving rise at first to a figure-of-eight loop and finally to a normal loop with the terminal limb posterior to the E point. The sense of rotation became counterclockwise (Figs. 1 and 4).

In the sagittal plane, the QRS loop became progressively more posterior, and the sense of rotation changed and became clockwise (Fig. 2). In the frontal plane, the QRS loop was displaced toward the left (Fig. 3).

TABLE II. ECG BEFORE AND AFTER SURGICAL CORRECTION FOR ATRIAL SEPTAL DEFECT

CASE	MONTHS AFTER SURGERY	ELECTRICAL AXIS		V_1 PATTERN		R/S OR R′/S IN V_1 (MM.)		R/S IN V_6 (MM.)		QRS INTERVAL (SEC.)		QRS COMPLEX	
		BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
1.	4	+90	+70	rsR′	RS	5/0	3/2.5	12/3	19/1	0.08	0.08	RVH	Not diagnostic
2.	7½	+120	++90	rSR′	rSr′	4/2.5	1.5/5	7/2	12/4	0.08	0.08	RVH	Normal
3.	8½	++110	++60	rSR′	rSr′	8/5	3/7	28/15	18/3	0.10	0.09	RVH	Normal
4.	6	++100	++80	rSr′	rSr′	2.5/3.5	2/8	19/8	15/6	0.08	0.08	Not diagnostic	Normal
5.	12	++100	++55	rSR′	rSr′	4/2	2.5/5	16/3.5	20/0	0.10	0.085	Not diagnostic	Normal
6.	8	++150	+120	rsR′	rsr′	10/1.5	2.5/2	13/8	21/7	0.09	0.08	RVH	Not diagnostic
7.	6	++90	++60	rSr′	rSr′	5/8	2/10	25/3	19/2.5	0.08	0.08	Not diagnostic	Not diagnostic
8.	7	−150	−30	rS	rS	8/13	1/5	9/6	15/8	0.07	0.07	RVH	Not diagnostic
9.	2	+120	+110	rsR′	rsR′	18/3	13/1	14/6	20/9	0.09	0.09	RVH	RVH
10.	1	+150	+120	Rs	rS	6/3	2.5/4	6/18	5/7	0.13	0.12	RVH + C.D.	Not diagnostic + C.D.
11.	7½	+120	+60	rSR′S′	rSr′	6/5	2/7	12/2	13/1	0.07	0.07	RVH?	Normal
12.	8	+125	+120	R	rsR′	12/0	9/.5	2/10	21/5	0.08	0.07	RVH	< RVH

RVH: Right ventricular hypertrophy. C.D.: Conduction delay. ?: Questionable diagnosis. <: Lesser degree.

TABLE III. VCG BEFORE AND AFTER SURGICAL CORRECTION FOR ATRIAL SEPTAL DEFECT

CASE	MONTHS AFTER SURGERY	SPATIAL ORIENTATION OF QRS LOOP*		ROTATION OF QRS LOOP IN HORIZONTAL PLANE		CONDUCTION DELAY		T LOOP		VCG DIAGNOSIS		DEGREE OF IMPROVEMENT	MONTHS FOR CLEAR CHANGES
		BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER		
1.	4	Ant. Rt.	Ant. Lt.	C.	C.C.			Opp.	A.D.	RVH	Normal?	Marked	1
2.	7½	Ant.	Ant. Lt.	C.	C.C.			Opp.	A.D.	RVH	– RVH	Marked	5½
3.	8½	Ant. Rt.	Ant. Lt.	C.	8			Opp.	A.D.	RVH	– RVH	Marked	7
4.	6	Ant.	Post. Lt.	8	C.C.			A.D.	Inc.	RVH	Normal	Normal	2
5.	12	Ant. Rt.	Lt.	8	C.C.	+	–	Opp.	Inc.	RVH	Normal?	Marked	5
6.	8	Ant. Rt.	Ant. Lt.	8	C.C.			Opp.	A.D.	RVH	Normal	Normal	2½
7.	6	Ant.	Ant. Lt.	C.	8			Opp.	A.D.	RVH	– RVH	Moderate	6
8.	7	Ant.	Lt.	C.	C.C.			Opp.	Inc.	RVH	Normal	Normal	3
9.	2	Ant.	Ant. Lt.	8	8	+	–	Opp.	Opp.	RBBB	RVH + C. del.	Moderate	2
10.	1	Ant. Rt.	Lt.	C.	C.C.	+		Opp.	Inc.	RVH + C. del.	Normal?	Marked	1
11.	7½	Ant.	Lt.	8	C.C.			A.D.	Inc.	RVH	Normal	Normal	3
12.	8	Ant. Rt.	Ant. Lt.	C.	C.			Opp.	A.D.	RVH	– RVH	Moderate	8

*Horizontal plane.

Ant.: Anterior. Post.: Posterior. Rt.: Right. Lt.: Left. C.: Clockwise rotation. C.C.: Counterclockwise rotation. 8: Figure-of-eight rotation. +: Presence of terminal conduction delay. C. del.: Presence of terminal conduction delay.

–: Less degree. Opp.: Opposite (in relation to QRS loop). A.D.: Angular deviation. Inc.: Included. RVH: Right ventricular hypertrophy. RBBB: Right bundle branch block.

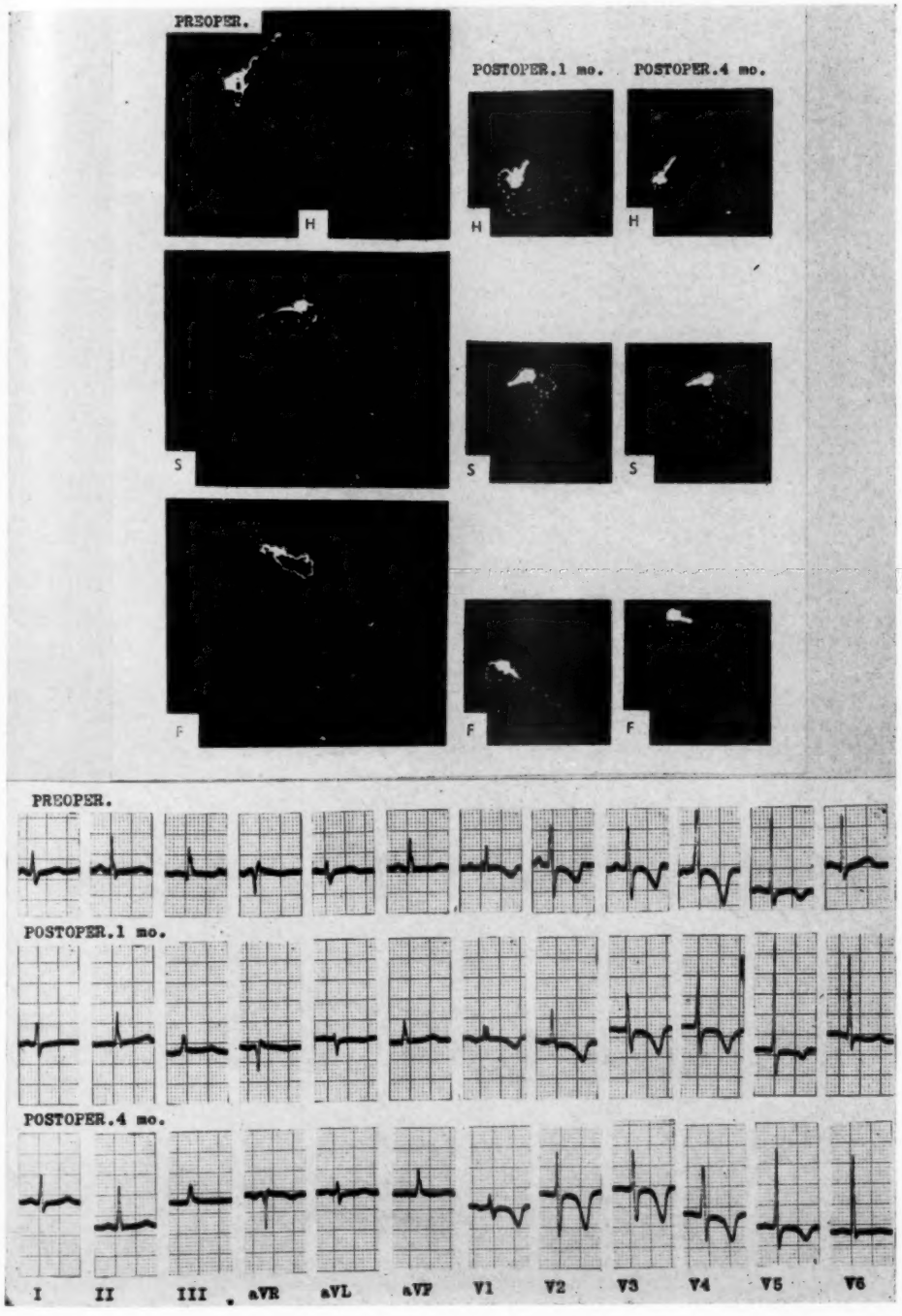

Fig. 2.—Case 1, M.B. The VCG shows marked normalization of the QRS loop following surgery. In the horizontal plane the terminal limb is displaced more posteriorly, and the sense of rotation has become counterclockwise. The sagittal plane clearly shows the change from a counterclockwise to a clockwise rotation following surgery. In the ECG the RSR′ pattern is replaced by an RS pattern.

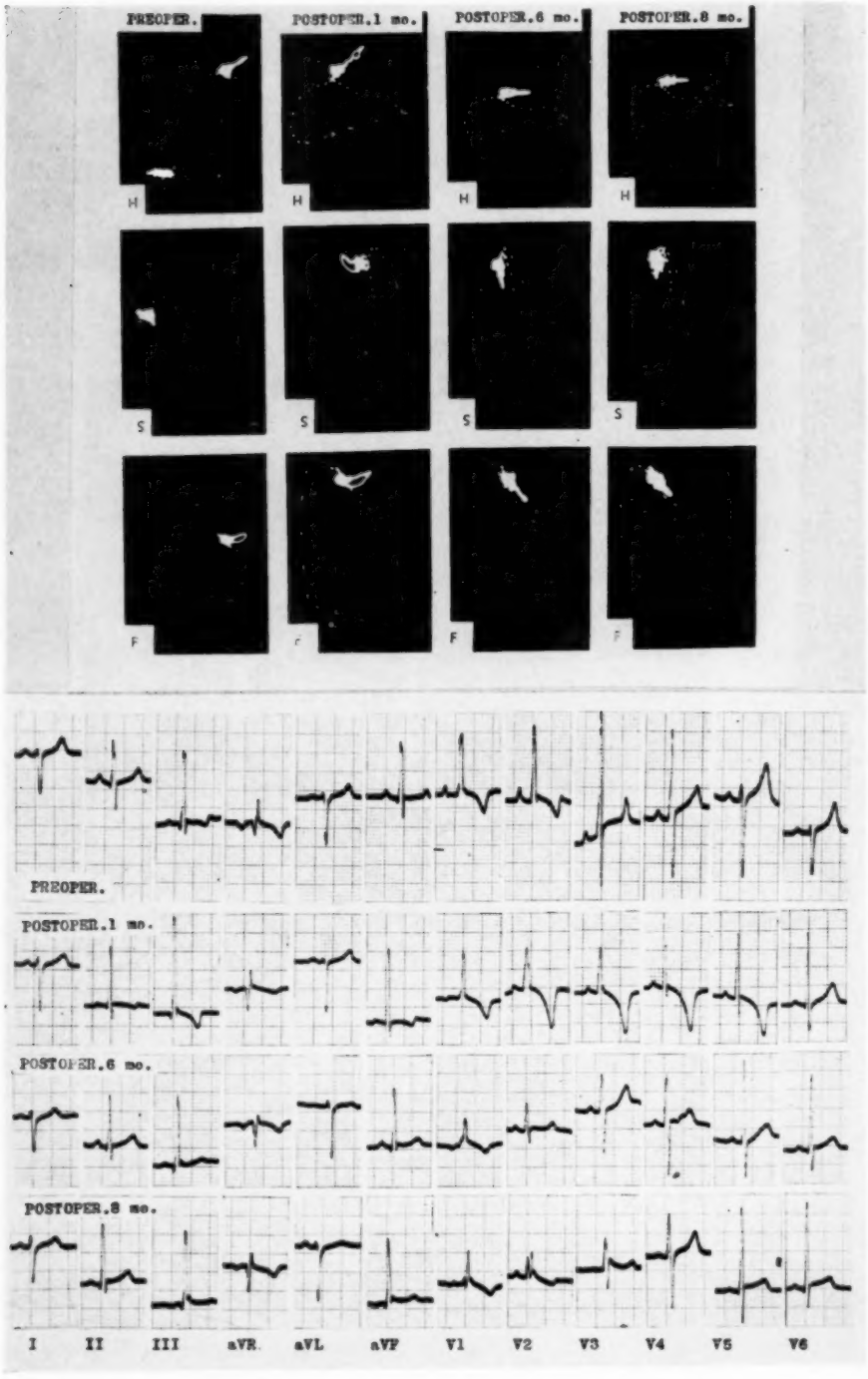

Fig. 3.—Case 12, L.W. Moderate postoperative improvement of the VCG. Prior to surgery, the QRS loop in the horizontal plane is markedly displaced anteriorly and to the right, explaining the presence of an R pattern in V_1. Postoperatively, the QRS loop in the horizontal and frontal planes shows a progressive displacement toward the left. There is a change in the ECG postoperatively: an R wave in V_1 changes to an RSR′ pattern, the amplitude of the QRS complex in V_1 is diminished, and the R wave in the left precordial leads increases.

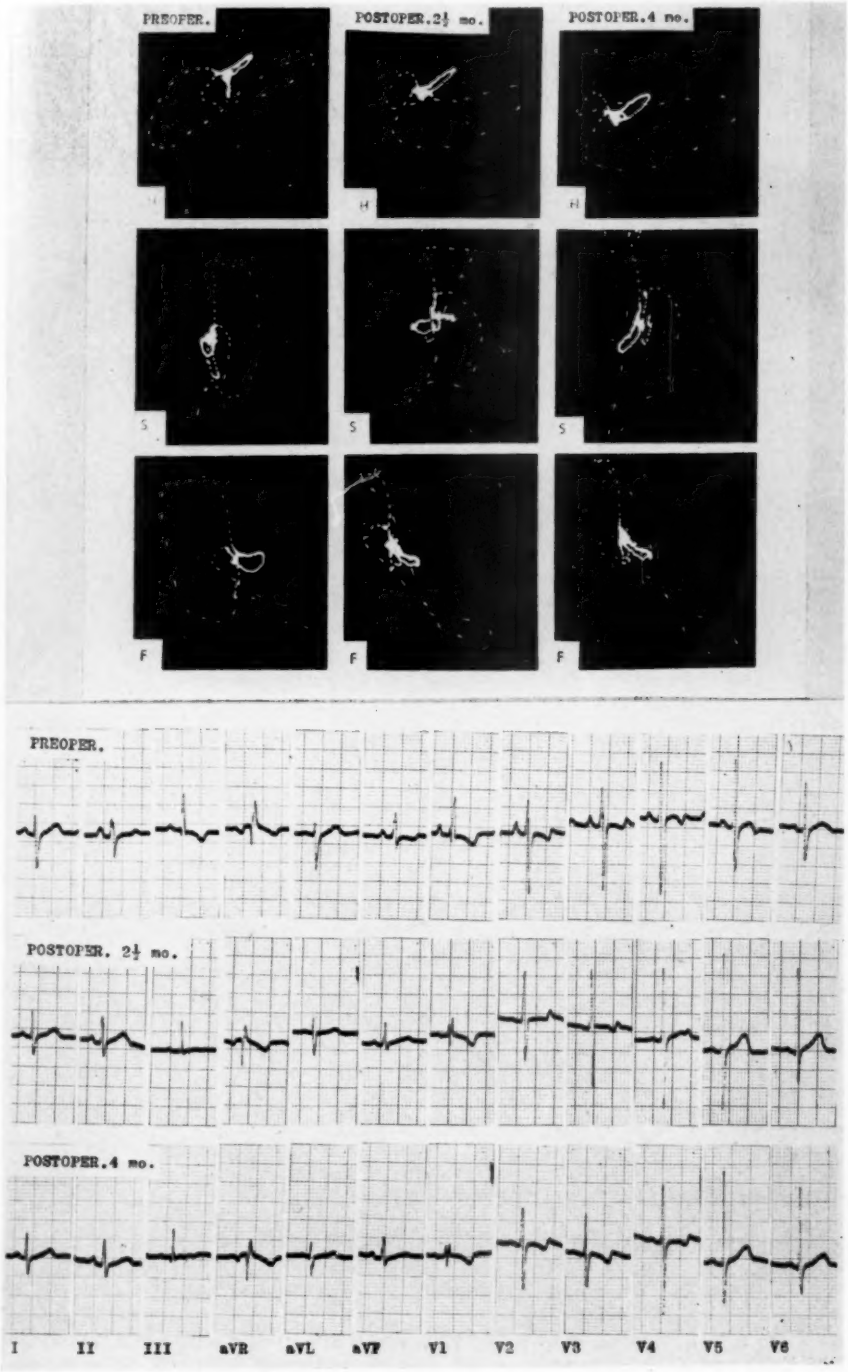

Fig. 4.—Case 6, C.M. Normalization of the QRS loop postoperatively. In the horizontal plane the QRS loop is displaced toward the left, and the terminal limb is progressively displaced posteriorly, becoming normal. There is diminution of the amplitude of the R′ pattern in V_1 and an increase in the amplitude of the R wave in V_6. The persistence of the RSR′ in V_1 following surgery, as demonstrated by the VCG, has an entirely different origin. Prior to operation it corresponds to a configuration of right ventricular hypertrophy, and to the projection of the terminal segment of the QRS loop, which is anteriorly placed and clockwise in rotation. After surgery, the terminal limb is normal in orientation and rotation, and the R′ corresponds to the projection of a normal vector.

In general, the T loop which was discordant to the QRS loop preoperatively changed to an angular deviation with the QRS loop and finally became concordant and was included in the QRS loop.

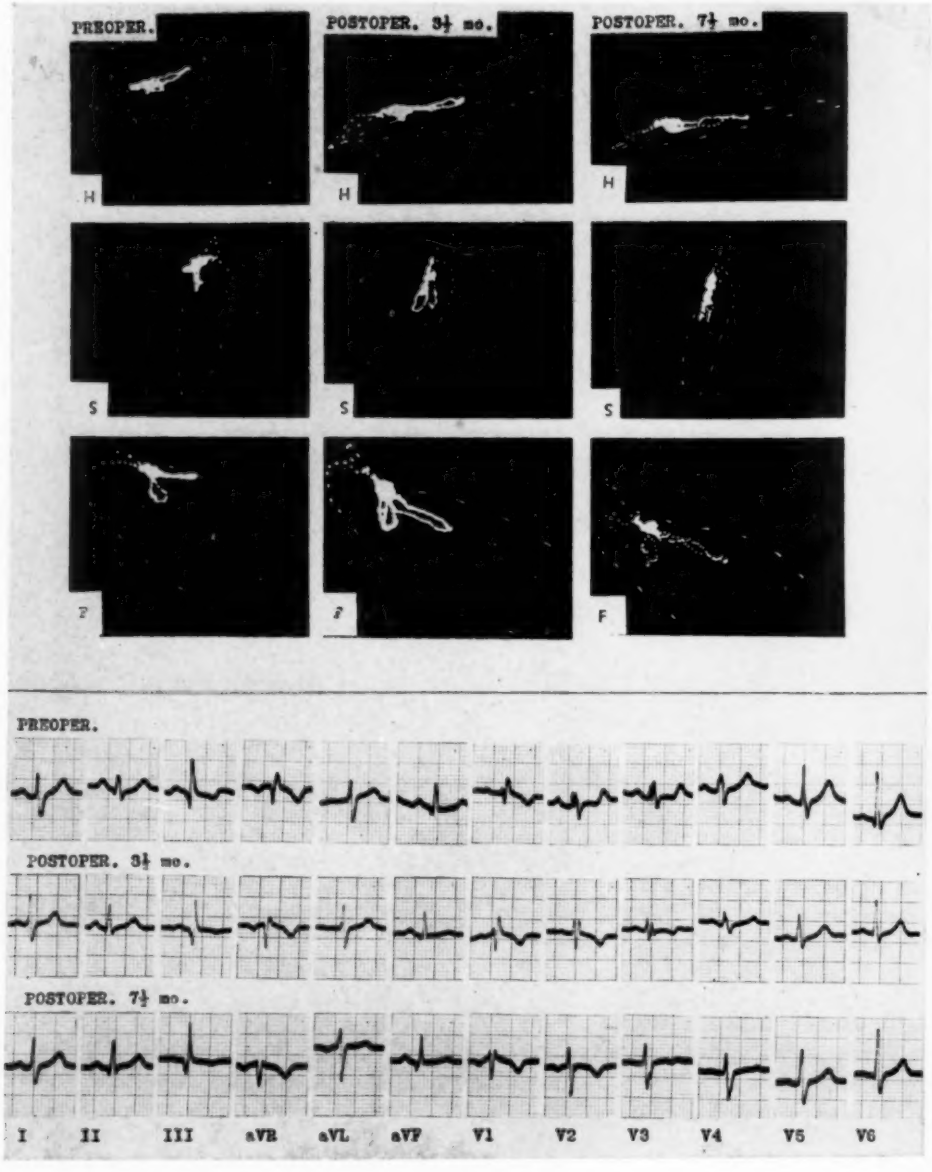

Fig. 5.—Case 2, R.E. Typical VCG configuration seen in a patient with atrial septal defect before surgery. The VCG and ECG show some of the changes previously described, following surgical correction.

In the cases demonstrating an intraventricular conduction defect prior to operation (Cases 5, 9, and 10), with a slowing in the terminal portion of the QRS loop, the postoperative vectorcardiograms demonstrated a diminution in the conduction defect.

When the degree of change was evaluated as being slight, moderate, marked, or as complete normalization (Table III), there was complete normalization in 4 cases (Fig. 1), marked improvement in 5 cases (Fig. 2), and moderate improvement in 3 cases (Fig. 3). The period of time between the surgical procedure and the appearance of clear-cut changes in the VCG was variable, usually several months. However, a marked and rapid regression in some cases, even within 4 weeks, was noted (Fig. 6).

Fig. 7 illustrates the sequence of changes toward normal in the vectorcardiogram. All of our cases belonged preoperatively to one of the first three patterns illustrated. Postoperatively, they all changed toward normal, in a variable degree and in the same sequence that is illustrated.

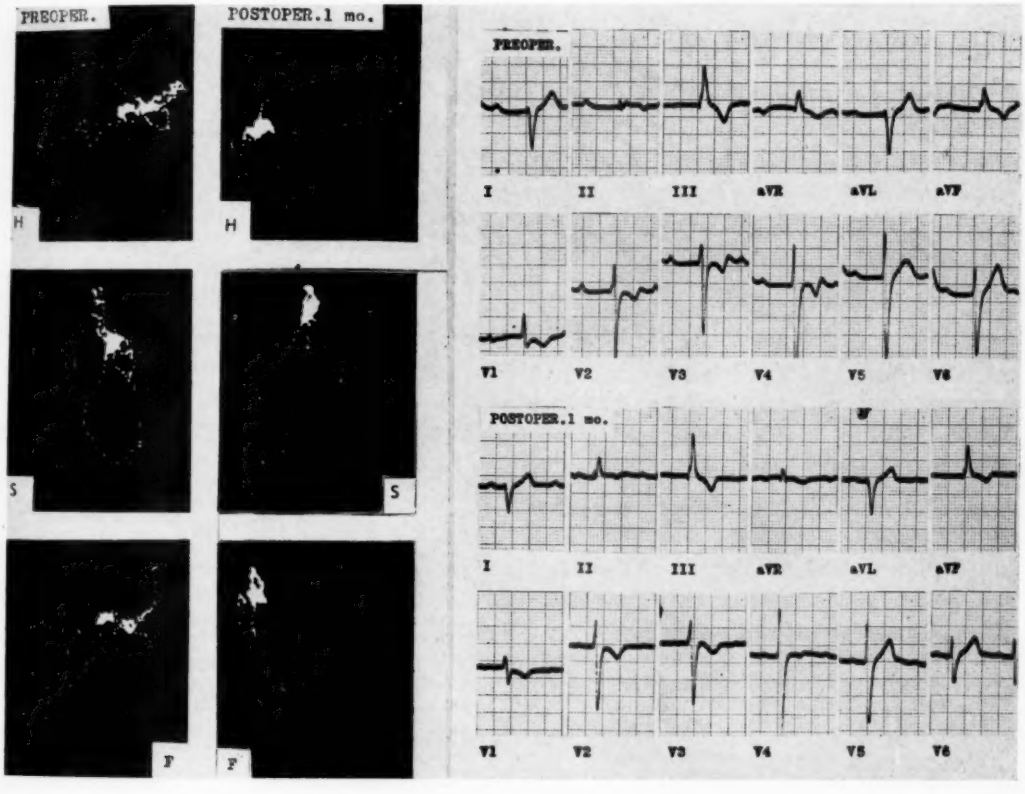

Fig. 6.—Case 10, A.M. This case illustrates a rapid change in the vectorcardiogram postoperatively. In the horizontal plane the QRS loop is displaced toward the right and clockwise in rotation preoperatively, and is normal 1 month postoperatively. There is also a diminution in the degree of conduction defect present.

DISCUSSION

Although the electrocardiogram and vectorcardiogram are often nonspecific in cases of congenital heart disease, they may be useful in following the progression of the anatomic and hemodynamic abnormalities toward normal after the surgical correction. In patients with pulmonary stenosis, Blount and asso-

ciates[8] and Kahn and associates[9] have shown progressively lesser degrees of right ventricular hypertrophy following valvulotomy. The same has been shown to be true in cases of atrial septal defect, with respect to electrocardiographic studies.[1-4] Our study confirms the electrocardiographic findings in patients with this type of malformation[10-13] and the changes that follow surgical correction of the secundum type of atrial septal defects. In addition, we are reporting the vectorcardiographic modifications.

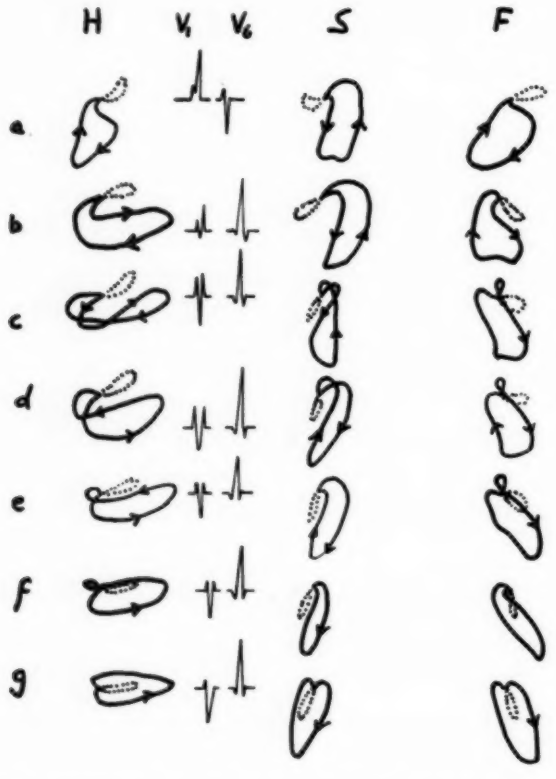

Fig. 7.—Diagrammatic representation of the progressive change in the three planes of the VCG and Leads V_1 and V_6 of the ECG following surgical correction of an atrial septal defect. Prior to surgery, all of the patients had QRS configurations conforming to either *a*, *b*, or *c*. Following surgery, serial vectorcardiograms showed a progression toward normal (*g*) that conformed to one of the patterns illustrated.

The period of follow-up was from 2 to 12 months; however, all of the patients have had an ECG and VCG at least every 2 months following surgery, so that the earliest changes would be detected. Significant changes were noted as early as 1 month and as late as 8 months after surgery. The average change occurred after 4 months. This is earlier than has been found in cases of pulmonary stenosis. Marked electrocardiographic and vectorcardiographic evidence of a lesser degree of right ventricular hypertrophy or complete normalization was noted in 9 of the 12 patients, and moderate improvement was noted in 3 others. It is possible that with a longer period of follow-up, complete normalization will occur in the majority. In Case 12, in which only a moderate improvement was noted after 8 months, there was a gradient of 50 mm. Hg across the pulmonary valve, indi-

cating some degree of pulmonary stenosis. However, another patient (Case 11) with a similar gradient showed complete normalization of the ECG and VCG after 6 months.

Although the ECG often shows marked changes following surgery, the RSR′ pattern usually persists, making a definite electrocardiographic diagnosis difficult. The VCG, on the other hand, shows clear-cut changes in the spatial orientation and rotation of the QRS loops (Fig. 7). Even with a normal configuration, the terminal limb, although posterior, may be oriented so that an electrocardiographic RSR′ pattern in Lead V_1 still persists. Therefore, before operation, the RSR′ results from the projection of an anterior and clockwise terminal limb, signifying right ventricular hypertrophy. After operation, the RSR′ results from the projection of a normal and posterior terminal limb.

The lesser degree of right axis deviation and increased voltage of the R waves in the left precordial leads are parallel with a shift of the QRS loop toward the left in the horizontal and frontal planes.

Since moderate changes occur early, and marked normalization is usually noted by 4 months, it appears that the ECG and VCG are useful in evaluating the success of surgery. There have been reports of cases in which recatheterization or reoperation actually demonstrated the persistence of a shunt when electrocardiographic abnormalities were not altered after surgery.[2,3,14]

From a theoretical standpoint, the changes in the ECG and VCG toward normal are an electrophysiologic expression of lesser degrees of right ventricular hypertrophy and may be useful in the understanding of the genesis of right ventricular hypertrophy and the RSR′ pattern. The various vectorcardiographic patterns that have been observed (Fig. 7) provide further proof that they represent an intermediate stage in the development of electrical signs of right ventricular hypertrophy. Furthermore, these patterns are not necessarily associated with right bundle branch block. The vectorcardiographic configurations also illustrate or explain how an RSR′ pattern may be an expression of right ventricular hypertrophy, an intermediate stage in the regression to normal, or an expression of projection of a normal vectorcardiographic QRS loop.

SUMMARY

1. Twelve cases of atrial septal defect of the secundum type have been followed from 2 to 12 months postoperatively, after surgical correction by direct vision, utilizing a pump-oxygenator bypass, in order to study electrocardiographic and vectorcardiographic changes.

2. The electrocardiographic changes consisted of a regression in the degree of right axis deviation, a smaller R or R′ in Lead V_1, and a taller R in Lead V_6. In the majority of cases an RSR′ pattern persisted.

3. The vectorcardiogram demonstrated gradual and marked changes toward normal. In the horizontal plane, before surgery, the QRS loop was displaced anteriorly, and to the right, with a clockwise sense of rotation. After surgery, the QRS loop became progressively more leftward, posterior, and the sense of rotation became counterclockwise.

4. The electrocardiogram and the vectorcardiogram provide a simple and reliable method of evaluating the regression of right ventricular hypertrophy toward normality in patients who have undergone corrective surgery for atrial septal defect.

We wish to express our gratitude to Dr. Alvin J. Gordon, who heads the Cardiac Catheterization Group, to Dr. Ivan D. Baronofsky, who performed the cardiac surgery, and to Miss Ruth Jaspan for her assistance in the preparation of this manuscript.

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Chronic Atrial Fibrillation Unrelated to Organic Heart Disease: Follow-Up Study of Five Cases

Elliott J. Howard, M.D., Bronx, N. Y.*

Chronic atrial fibrillation is usually a manifestation of heart disease, thyrotoxicosis with heart disease, or drug intoxication. However, on rare occasions, prolonged chronic atrial fibrillation may be unrelated to an underlying organic state. Paroxysmal atrial fibrillation secondary to various stresses, such as tobacco, alcohol, trauma, violence, excitement, thoracic surgery, and pneumonia, is a common phenomenon.

Friedberg[1] states that 5 or 6 per cent of the cases of atrial fibrillation are chronic and of nonorganic etiology. White[2] and Katz and Pick[3] in their textbooks agree that the patient with a hypersensitive, neurotic personality is predisposed to chronic atrial fibrillation. Wolff[4] reported five cases of atrial fibrillation with a familial incidence. In one family, three brothers had chronic atrial fibrillation, and two brothers of another family had the paroxysmal variety. Orgain, Wolff and White[5] reported 49 cases of this arrhythmia without evidence of cardiac disease, three of them were chronic, and two others had both fibrillation and flutter. Hanson and Rutledge[6] reviewed 651 cases of atrial fibrillation and found 30 (4.6 per cent) to be in patients with normal hearts. Ten (1.5 per cent) were of the chronic variety. Phillips and Levine[7] found a higher incidence of chronic fibrillators, noting 61 of 84 patients with atrial fibrillation who had no evidence of organic heart disease. The average age was 50 years, which is higher than that which others report. They also studied the duration of regular rhythm following conversion with quinidine and found that 88.5 per cent were able to be converted to a regular rhythm. The younger patients maintained the regular rhythm longer than did the older patients (61.4 months in the younger group; 21 months in the older group). The duration of regular rhythm seemed to be related to the length of time that fibrillation had previously been present. Those with fibrillation for over 1 year maintained a regular sinus rhythm for much shorter periods. Six of their patients had advanced congestive heart failure which proved to be completely reversible upon conversion to normal sinus rhythm. The absence of peripheral embolization and rapid ventricular rates is contrasted to their common occurrence in atrial fibrillation associated with heart disease.

From the Medical Service of the Bronx Veterans Administration Hospital, Bronx, N. Y.
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*Present address: 630 Park Ave., New York, N. Y.

Five cases of chronic atrial fibrillation in patients with neurotic personality traits are being reported. Four of these patients have been observed regularly for more than 13 years since the onset of the arrhythmia. The fifth has been followed for 11 months. Thorough investigation of the history, physical examination, electrocardiogram, chest x-ray, radioactive iodine studies, and basal metabolic rates were made but failed to disclose an etiology for heart disease, thyroid disease, or intoxicating agent. Each of the patients described himself as being of the "very nervous type," and three of them were given a diagnosis of "psychoneurotic anxiety state" by psychiatrists. The fourth was described by his attending physician as having a "difficult emotional problem." Characteristic traits in one or more of these patients include smoking three packs of cigarettes and drinking fifteen cups of coffee daily, feelings of sexual inadequacy, divorce, mother complexes, rigid personality and schizophrenic behavior patterns.

Age at onset varied from 28 to 53 years. In each case, quinidine either failed to convert the fibrillation or failed to maintain the sinus rhythm for more than short periods. Each patient was given digitalis to control the ventricular rate, and four of them have been kept on maintenance therapy. Symptoms and complaints are limited to nervousness and occasional shortness of breath. None complained of orthopnea or dyspnea on exertion. Three continue to undertake strenuous occupations, and the other two engage in more than average activity, without disability. Electrocardiograms and chest x-ray for cardiac configuration taken at the time of onset of the arrhythmia compared to those taken recently do not demonstrate any significant change except for some left ventricular enlargement in one case (Case 2).

CASE REPORTS

CASE 1.—H.M. is a 52-year-old married man. Cardiac dysrhythmia was noted when he was 38 years old in 1945, while he was in the military service. The presenting symptoms were dyspnea and nervousness. During the first 3 years the heart rhythm varied between atrial fibrillation, flutter-fibrillation, and, occasionally, complete heart block. Subsequently, the arrhythmia was confined to chronic atrial fibrillation, persisting to the present time. The physical examination at the time of admission to the Bronx Veterans Administration Hospital in August, 1948, was within normal limits except for the irregular heart rhythm. His attending physician observed that the patient had a "difficult emotional problem." The chest x-ray was normal. The basal metabolic rate was −4 per cent and serum cholesterol was 266 mg. per cent. He is currently employed in moderately active work with the post office, and he participates regularly in the game of handball. Electrocardiogram and heart size have remained unchanged since the onset of the arrhythmia. Present symptoms are limited to occasional shortness of breath, which he relates to nervousness. He is seen regularly at half- to one-year intervals.

CASE 2.—S.S. is a 47-year-old three-time divorced man. He is a bookseller whose particular field requires frequent overseas travel. When first seen in 1946, at the age of 34, he gave a history of dyspnea and palpitation of 3 years' duration. He was found to have paroxysmal atrial fibrillation which had occurred daily in spite of quinidine therapy (1.6 Gm. daily) for an 18-month period. The arrhythmia became permanent in 1953, and has persisted to the present time. Physical examination at the time of admission to the Bronx Veterans Administration Hospital in October, 1946, was normal except for the atrial fibrillation and an acute cystitis. Chest x-ray was normal. The basal metabolic rate was −5 per cent and +3 per cent. Psychological testing, carried out because of obvious personality disorder, revealed a "rigid personality and schizophrenic behavior pattern." He was found to be in frank congestive heart failure in December, 1956, and therefore

was placed on permanent digitalis therapy at that time. X-ray of the heart has remained unchanged since 1953, but there has been some left ventricular enlargement when comparison is made with the x-ray recorded in 1946. The electrocardiogram has remained essentially unchanged. He is examined periodically every 6 to 12 months.

CASE 3.—G.M. is a 44-year-old married man. He was found to be fibrillating when he was admitted to the Bronx Veterans Administration Hospital in February, 1946, with the complaint of shortness of breath. His occupation was (and is) roof waterproofing. During the first 6 years the cardiac rhythm varied between sinus rhythm, atrial flutter, and atrial fibrillation while he was on maintenance quinidine therapy (1.6 Gm.). Since that time, atrial fibrillation has been permanent. Paroxysms of rapid ventricular response (150 per minute) with frequent extrasystoles prompted digitalization in August, 1955. Digitalis has been maintained to the present time. Psychiatric examination termed the patient as being in a psychoneurotic anxiety state. His laboratory data in 1946, included a basal metabolic rate of +15 per cent and +27 per cent, and a serum cholesterol of 132 mg. per cent. The chest x-ray was normal. In 1952, the radioactive iodine uptake in 24 hours was 42 per cent, the basal metabolic rate was 22 per cent, and the serum cholesterol was 125 mg. per cent. At present, the patient continues his active occupation, and complains of shortness of breath related only to his nervousness. Electrocardiogram and chest x-ray remain essentially unchanged from the original studies.

CASE 4.—V.G. is a 28-year-old married truck driver. He was admitted to the Bronx Veterans Administration Hospital in October, 1958, for evaluation of an irregular cardiac rhythm. He was symptom-free. History elicited the facts that he habitually smoked three packs of cigarettes and drank twelve to fifteen cups of coffee daily. The use of drugs (including the amphetamines, which are often used by long-distance truck drivers) was denied. The patient received a psychiatric discharge from the military service during World War II. Physical examination was normal except for atrial fibrillation and an obvious nervousness. The basal metabolic rate was +15 per cent, the serum cholesterol was 230 mg. per cent, and the 48-hour uptake of radioactive iodine was 25 per cent. The chest x-ray was within normal limits. The patient was observed for several weeks, during which time he was restricted from smoking and limited to one cup of coffee a day. Attempts at converting his rhythm to normal with 3 Gm. of quinidine failed. He was digitalized to slow the ventricular rate. He has now been observed for 11 months. The fibrillation has been constant and the electrocardiogram and chest x-ray are unchanged.

CASE 5.—R.P. is a 63-year-old male janitor. Atrial fibrillation was first noted in 1949, when he visited his private physician for complaints of headache, abdominal pains, sexual inadequacies, and shortness of breath. The patient was not aware of his irregular rhythm. The complaints have subsequently been evaluated and are regarded as being related to his psychoneurotic anxiety state. At the time of his first examination, all findings were normal except for the cardiac arrhythmia, slight enlargement of the left ventricular inflow tract, moderate obesity, and acute cystitis. Quinidine therapy was given almost continuously in varying dosages up to 2 Gm. daily for an 8-year period, but a regular sinus rhythm occurred only intermittently for days, and sometimes months. In March, 1957, quinidine maintenance was discontinued, and digitalis therapy was begun in order to control the ventricular rate. In June, 1959, the patient had been fibrillating continuously for 30 months and was still on digitalis therapy. Chest x-ray and electrocardiogram are unchanged from those taken in 1949.

COMMENT

We are speculating that in the five reported cases of chronic atrial fibrillation, organic heart disease does not exist. The final proof must await histopathologic examination.

In Cases 2 and 5, congestive heart failure and left ventricular enlargement were noted. In the first instance these complications appeared 10 years after the onset of the arrhythmia, and in both cases there was a rapid ventricular rate. It was felt that these complications were directly related to the reduced cardiac efficiency resulting from a rapid ventricular rate.[3]

Some of the studies relating to thyroid function in Case 3 are suggestive of hyperthyroidism. However, the absence of confirmatory evidence by history or physical examination, and normal results on two occasions with radioactive iodine uptake studies preclude a diagnosis of thyrotoxicosis.

In Case 4, the atrial fibrillation was at first thought to be related to the large quantities of coffee and cigarettes consumed. However, after a long period of abstention from the use of these agents, the arrhythmia persisted, and it was felt that these excesses represented the patient's personality defect rather than etiologic agents.

SUMMARY

Five cases of chronic functional atrial fibrillation observed for periods ranging from 11 months to 14 years are reported. Evidence for organic heart disease has not been substantiated. Four of the patients require permanent digitalis therapy, one of whom had been in frank congestive failure. Each of the patients reported has a personality disorder confirmed by psychiatric evaluation.

The literature pertaining to idiopathic atrial fibrillation has been reviewed.

The advice and guidance of Dr. Walter Newman, Assistant Chief, Cardiac Section, Bronx Veterans Administration Hospital, is gratefully acknowledged.

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The Electrocardiogram in Pulmonary Stenosis With Intact Septa

Lamberto G. Bentivoglio, M.D., Vladir Maranhao, M.D., and Daniel F. Downing, M.D., Philadelphia, Pa.

To determine the electrocardiographic patterns in pure pulmonary stenosis, i.e., pulmonary stenosis with intact atrial and ventricular septa, the tracings of 100 consecutive individuals with the defect were studied.

MATERIAL AND METHOD

There were 43 males and 57 females. The age ranged from 4 months to 50 years, the average being 11 years. Seventy were under 10 years of age.

In each patient a gradient in systolic pressure was demonstrated by withdrawal of a cardiac catheter from the pulmonary artery to the right ventricle. When a small gradient was shown, the maneuver was repeated two or three times in order to rule out artefact. In order to encompass the gamut of variation, no minimum limit was placed upon the magnitude of the gradient for the study. However, except in 2 patients, one with a gradient of 5 mm. Hg and one with a gradient of 8 mm. Hg, the difference in systolic pressure between vessel and chamber was over 10 mm. Hg.

Anyone in whom there was even a suggestion of a left-to-right shunt at any level was excluded from consideration, as were those with arterial unsaturation. Excluded, too, were patients with no shunt but in whom the catheter tip passed from the right atrium to the left atrium, presumably through a patent foramen ovale.

Routine twelve-lead electrocardiograms were obtained in all patients. In 55, Lead V_{3R} or Lead V_{4R} was also recorded. The electrical axis of P, R, and T was measured by Carter's method.[1] The normal axis of P was concluded to lie between $+45°$ and $+69°$; that of QRS between $+30°$ and $\pm 90°$. The value of the T axis was approximated to the nearest angle multiple or submultiple of 15°. Electrical position was determined by the criteria of Wilson.[2] Duration, magnitude of deflection, and ventricular activation time were calculated according to the recommendations of the Committee on Electrocardiography of the American Heart Association.[3]

The data were analyzed in relation to right ventricular pressure, and patients were divided into four groups. Group I: Right ventricular pressure to 35 mm. Hg (23 patients). Group II: Right ventricular pressure between 36 and 60 mm. Hg (25 patients). Group III: Right ventricular pressure between 61 and 110 mm. Hg (27 patients). Group IV: Right ventricular pressure above 110 mm. Hg (25 patients).

RESULTS

The P wave was not remarkable in regard to axis (Fig. 1) or duration in any group. Its amplitude was 3 mm. in Lead II in one patient with a systolic

From the Departments of Medicine and Pediatrics, Hahnemann Medical College and Hospital, Philadelphia, Pa.

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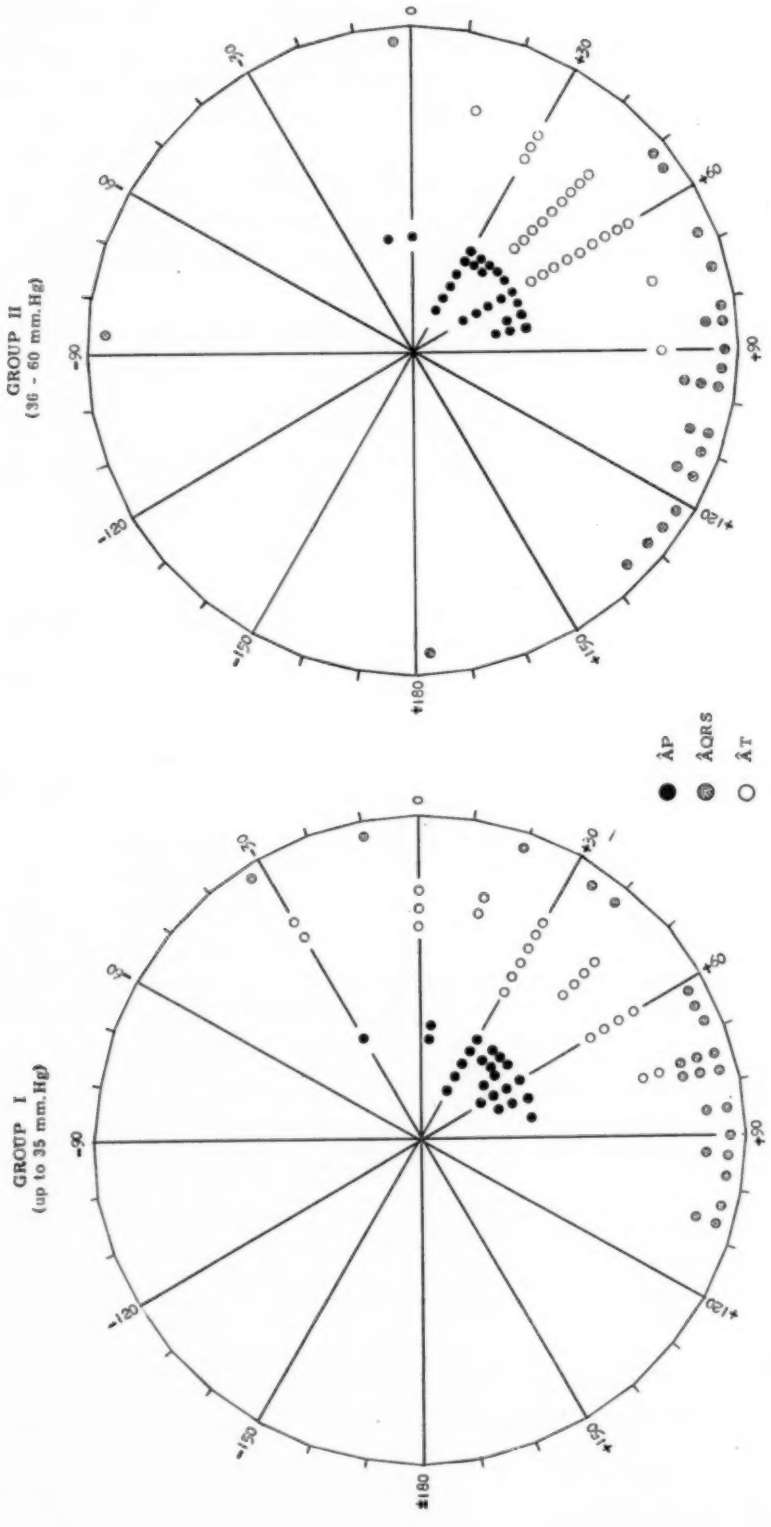
GROUP II
(36 - 60 mm.Hg)
GROUP I
(up to 35 mm.Hg)
ÂP
ÂQRS
ÂT
0
+30
+60
+90
+120
+150
±180
-150
-120
-90
-60
-30

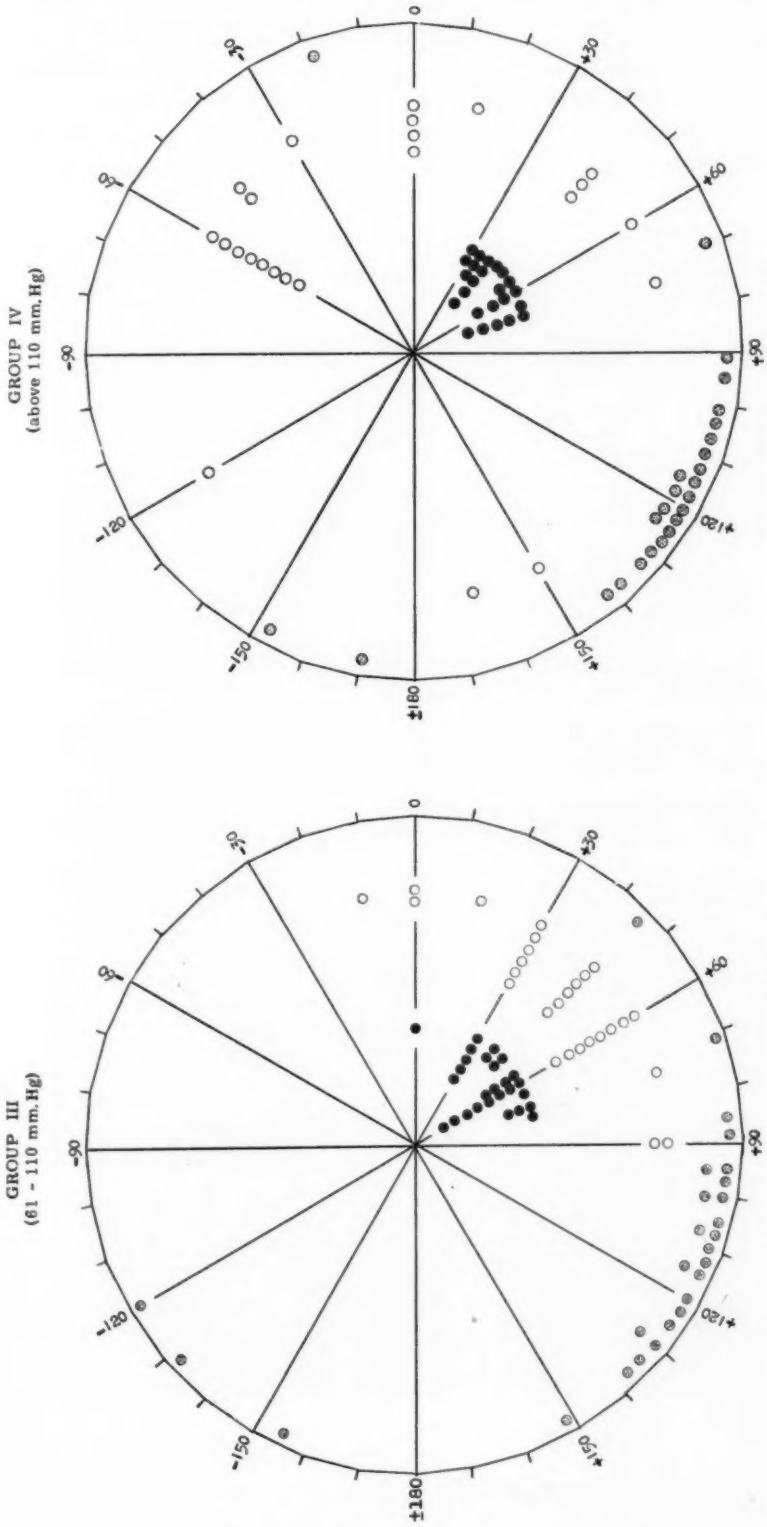

Fig. 1.—Frontal plane distribution of the mean manifest electrical axis of atrial ($\bar{A}P$) and ventricular ($\bar{A}QRS$) depolarization and ventricular repolarization ($\bar{A}T$).

pressure of 80 mm. Hg in the right ventricle. In Group IV, the amplitude was 3 mm. or more in Leads II, V_1, and V_2 in 8 patients and invariably was peaked. Pointed or rounded waves prevailed in the peripheral leads, and pointed, diphasic, or rounded waves prevailed in the precordial leads of this group.

The P-R interval was prolonged in 2 patients. It was abnormally short in one individual with the Wolff-Parkinson-White phenomenon. All were in Group III.

The axis of QRS was normal in 61 per cent of Group I, 32 per cent of Group II, 18 per cent of Group III, and 4 per cent of Group IV. Left axis deviation was present in 3 patients of Group I, and in 1 patient of Group IV, the patient with the Wolff-Parkinson-White phenomenon (Fig. 1).

Electrical position was vertical or semivertical in 77 per cent of Group I, 44 per cent of Group II, 27 per cent of Group III, and 4 per cent of Group IV.

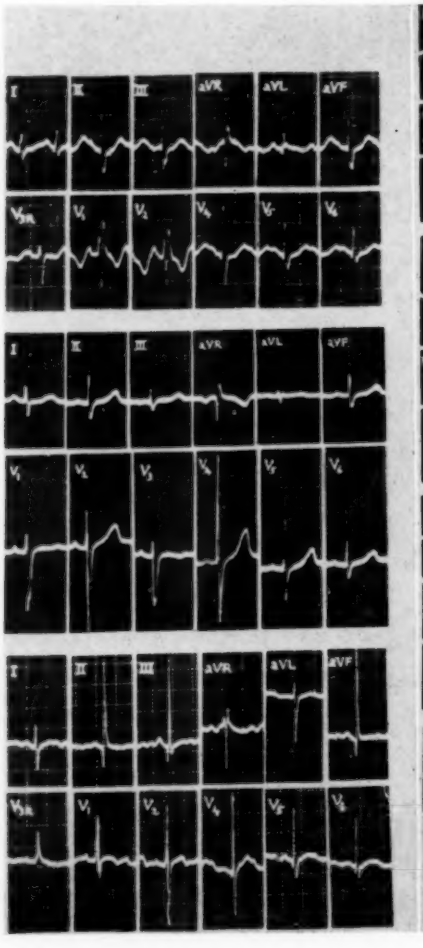

Fig. 2.

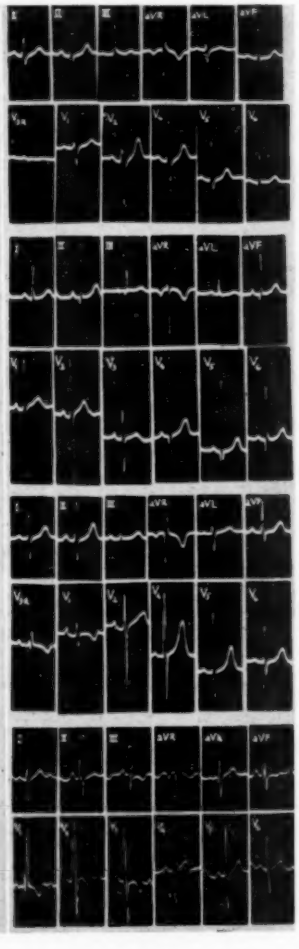

Fig. 3.

Fig. 2.—Representative tracings from Group I, with right ventricular pressure to 35 mm. Hg.
Fig. 3.—Representative tracings from Group II, with right ventricular pressure between 36 and 60 mm. Hg.

Horizontal or semihorizontal position progressed in frequency from 13 per cent in Group I to 84 per cent in Group IV.

QRS duration was normal in but 4 patients, Group I not being represented.

Ventricular activation time was prolonged with increasing frequency, ascending through the groups: in Lead V_{3R} from 40 per cent to 70 per cent, and in Leads V_1 and V_2 from 22 per cent to 96 per cent. It was normal in Lead V_6 in all but one patient, this one being in Group IV.

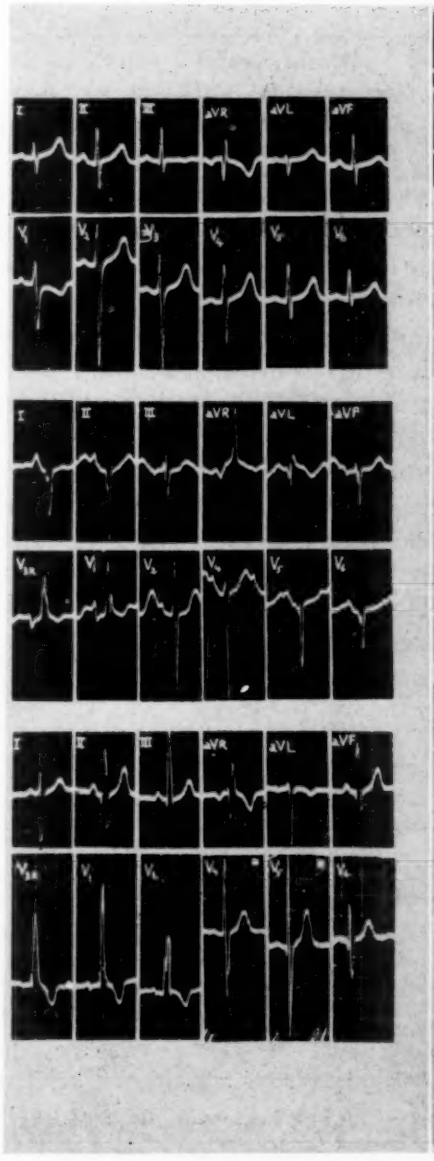

Fig. 4.

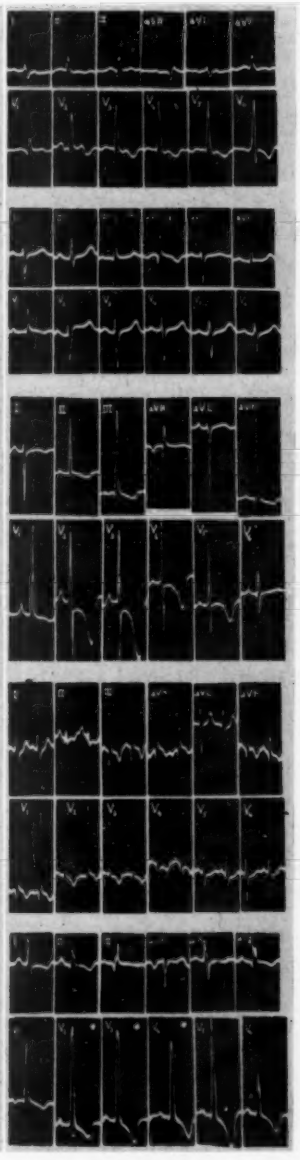

Fig. 5.

Fig. 4.—Representative tracings from Group III, with right ventricular pressure between 61 and 110 mm. Hg.

Fig. 5.—Representative tracings from Group IV, with right ventricular pressure above 110 mm. Hg.

TABLE I. GROUPING OF PATIENTS ACCORDING TO RIGHT VENTRICULAR PRESSURE AND AGE

RIGHT VENTRICULAR PRESSURE (MM. Hg)	AGE GROUPS					TOTAL FOR RIGHT VENTRICULAR PRESSURE
	0–1	1–5	5–20*	20–30	30–40†	
Up to 35	5	8	10	–	–	23
36–60	4	9	9	3	–	25
61–110	4	6	9	6	2	27
Above 110	1	3	8	7	6	25
Total for age	14	26	36	16	8	100

*The age group 10 to 20, being unusually small and showing no appreciable difference from the preceding group, is added to the latter, the two being considered together.

†The age group 30 to 40 also includes one 50-year-old patient.

A Q wave was present in Lead V_6 in 74 per cent of Group I, 44 per cent of Groups II and III, and 24 per cent of Group IV. In 5 patients in the first three groups it measured 4 mm.

Through the four groups the amplitude of R increased in Lead V_{3R} from an average of 7.7 mm. to 29 mm., in Lead V_1, from 12 to 20 mm., and in Lead V_2, from 13 to 20 mm. In Lead V_6 the average height was constant, the range of average being 10 to 8 mm.

The S wave showed increased prolongation in Leads I and V_6 from the low-pressure to the high-pressure groups. Slurring was noted more frequently as pressure increased. Absence of the deflection in the right precordial leads was noted with greater frequency as right ventricular pressure increased; in Lead V_6 it tended to be present more often in this circumstance. In the right precordial leads its amplitude tended to decrease as right ventricular pressure increased; in Lead V_6 the height was constant.

TABLE II

GROUPS OF PRESSURE (MM.Hg)	P WAVE		P-R INTERVAL	QRS COMPLEX								
				DURATION								
	DURATION	VOLTAGE		QRS INTERVAL				VENTRICULAR ACTIVATION TIME			S WAVE	
				PERIPHERAL BIPOLAR	V_{3-4R}	V_1	V_2	V_{3-4R}	V_1	V_2	I	V_6
Up to 35	0.074	1.11	0.128	0.068	0.067	0.068	0.070	0.028	0.027	0.021	0.023	0.022
36–60	0.082	1.30	0.140	0.074	0.066	0.070	0.068	0.033	0.034	0.027	0.030	0.023
61–110	0.084	1.54	0.140	0.080	0.070	0.075	0.076	0.043	0.043	0.034	0.033	0.026
Above 110	0.092	2.04	0.160	0.086	0.070	0.080	0.080	0.037	0.053	0.040	0.041	0.034

The ratio of R to S was 1 or greater in the right precordial leads, with increasing frequency as right ventricular hypertension became more marked. The mean ratio in Lead V_6 decreased from Group IV to Group I. The $\frac{R/S_{V5-6}}{R/S_{V1}}$ ratio decreased from Group I to Group IV.

The sum of deflection of R_{V1} and S_{V5-6} showed a gradual increase, and that of R_{V5-6} and S_{V1} a gradual decrease from Group I to Group IV.

RS complexes of greater than 50 mm. in Leads V_2 and V_3 were present in a few patients in each group.

The shape of the QRS complex in the right precordial leads varied. In general, the R component was prominent in all pressure groups, assuming greater amplitude or greater purity as right ventricular pressure increased.

RS-T segment depression was present in Leads II and aVF in one child, and in Leads V_1 and V_2 in another of Group III. In Group IV, depression was seen in 64 per cent, usually in multiple limb and precordial leads.

The axis of T showed a progressive shift to the right, parallel to the axis of QRS in Groups I and II. In Group IV there was a tendency toward opposition of these axes (Fig. 1).

Inversion of T from Lead V_{4R} to Lead V_2, and occasionally to Lead V_3, was very common in the first three groups. In Group IV this was constant, frequently marked, and of the "ischemic" type.

Prolongation of the Q-T interval was observed in a few individuals in each group, most often in Group IV.

Representative tracings from each group are shown in Figs. 2 through 5.

COMMENT

With advancing age, there was a significant gradual increase in right ventricular systolic pressure and in the systolic pressure gradient across the pulmonic

QRS COMPLEX													
VOLTAGE												R.V. PRESSURE (AVERAGE)	R.V.—P.A. MEAN SYSTOLIC EJECTION PRESSURE GRADIENT
R WAVE			S WAVE			R/S RATIO			$\frac{R/S_{V5-6}}{R/S_{V1}}$	$R_{V1}+S_{V5-6}$	$R_{V5-6}+S_{V1}$		
V_{2-4R}	V_1	V_6	V_{2-4R}	V_1	V_6	V_{2-4R}	V_1	V_6					
4.05	7.00	11.00	4.06	8.00	2.22	1.06	1.30	8.60	11.40	9.66	19.18	28/0	13
8.13	10.80	10.30	5.05	7.03	5.00	3.04	4.45	4.24	5.06	14.00	15.30	47/0	29
10.40	12.50	7.63	2.40	5.35	5.39	6.25	7.77	2.20	2.20	18.30	11.62	92/1	77
26.00	20.60	4.85	—	2.70	7.23	—	13.00	1.78	0.53	28.00	9.00	146/4	129

valve (Table I). This is believed to indicate a relative rather than an absolute increase in the degree of obstruction. The orifice remains the same size, but the greater capacity of the right ventricle and the greater blood volume and stroke volume of older individuals necessitates generation of higher ejection pressure.

Certain measurements in the electrocardiogram showed a progressive increase in magnitude through the groups as the severity of the stenosis and pressure in the right ventricle became greater: mean duration and amplitude of P, duration of P-R, duration of QRS (more pronounced in the peripheral and bipolar leads and in Lead V_1), ventricular activation time in the right precordial leads, amplitude of R in Leads V_{3R} and V_1, duration of S in Leads I and V_6, amplitude of S in Lead V_6, R/S ratio in Leads V_{3R} and V_1, the sum of R_{V1} and $S_{V5\text{-}6}$.

There was a definite inverse relationship between the amplitude of R in Lead V_6, that of S in Lead V_1, the ratio $\frac{R/S_{V5\text{-}6}}{R/S_{V1}}$, the sum of $R_{V5\text{-}6}$ and S_{V1}, and the right ventricular systolic pressure (Tables III and IV).

The incidence of a Q wave in Leads V_{3R} and V_1 increased through the four pressure groups: 1 patient in Group I, 2 in Group II, 5 in Group III, 9 in Group IV (Tables II and III).

In regard to the shape of QRS in Leads V_{3R} and V_1, there was a predominance of the R type in the entire series (Table IV). As the pressure increased, this deflection also increased in prominence, and S decreased almost to extinction. Q was present in a large number in Group IV only (Table I). The pattern of so-called right bundle branch block was uncommon. We can offer no proof, but believe that this rarity reflects a lack of right ventricular dilatation in this defect.

DISCUSSION

At least two studies of the electrocardiogram in pulmonary stenosis in series of a size similar to ours have been reported, those of Sodi-Pallares and associates[4] and Cayler and associates.[5] No strict comparison can be made because in our study we have evaluated only patients with both septa intact, and because we have included 8 individuals without right ventricular hypertension. However, the areas of comparability are sufficiently wide so that certain differences are significant.

One gains the impression from the report of Sodi-Pallares that patients with what is defined as "slight" pulmonary stenosis (right ventricular pressure up to 90 mm. Hg) will have a normal electrocardiogram or one with slight alteration. Our data indicate that the majority with pure pulmonary stenosis of any degree (even patients in our Group I with right ventricular systolic pressure below 35 mm. Hg) have abnormal tracings. Of the 100 patients evaluated, evidence of right ventricular hypertrophy in the right precordial leads was found in 60 per cent of Group I, 76 per cent of Group II, 85 per cent of Group III, and 100 per cent of Group IV. Our criteria of right ventricular hypertrophy in this study have been, simply, either an R/S ratio greater than 1 or a pure, notched, or slurred R in Leads V_{4R}, V_{3R}, or V_1. Objection may be made on the basis of assertions that such patterns are normal in infants—and several of our patients

TABLE III. COMPARISON OF THE INCIDENCE OF SOME NORMAL AND ABNORMAL ELECTROCARDIOGRAPHIC FINDINGS IN THE DIFFERENT PRESSURE GROUPS

	RIGHT VENTRICULAR SYSTOLIC EJECTION PRESSURE			
	UP TO 35 MM. Hg (%)	36–60 MM. Hg (%)	61–110 MM. Hg (%)	ABOVE 110 MM. Hg (%)
P wave ≥ 3 mm. and peaked	—	—	4	28
Prolonged P-R interval	—	—	—	8
Right axis deviation	26	56	85	92
Electrical position:				
Vertical	83	44	26	4
Indeterminate	—	44	37	8
Horizontal	17	8	34	84
Prolonged V.A.T. in V_{3R} and/or V_1	44	56	85	96
Presence of Q wave:				
Lead V_1	4	8	22	40
Lead V_6	74	44	44	24
Increased R/S_{V1} ratio*	4	21	60	100
Decreased R/S_{V6} ratio†	—	16	40	83
RS-T segment depression in leads facing the right ventricle	—	—	7	64
T-wave inversion in leads facing the right ventricle	—	—	—	100

*In cases with S wave in Lead V_1.
†Only those cases were considered in which Lead V_6 records left ventricular potentials.

TABLE IV. DISTRIBUTION OF QRS PATTERNS IN THE PRESSURE GROUPS

BASIC PATTERN	PRESSURE GROUPS			
	I: UP TO 35 MM. Hg	II: 36–60 MM. Hg	III: 61–110 MM. Hg	IV: ABOVE 110 MM. Hg
	LEAD V_1			
qR R Rs	qR 1 R 1 RR′ 1 rR′ 3 rsR′ 2	qR 1 qRs 1 R 1 RR′ 1 Rn 2 Rns 2 rsR′ 4	qR 5 R 2 RR′ 1 Rn 4 Rns 1 rR′ 4 Rsr′ 1 rsR′ 2	qR 6 qRn 2 qRS 1 R 9 Rn 3 Rns 1
Number–Percentage	8 35%	12 48%	20 74%	22 88%
RS	RS 9	RS 7	RS 5	RS 3
Number–Percentage	9 39%	7 28%	5 19%	3 12%
rS	rs 1 rS 5	rS 4 rnS 1 rSr′ 1	rS 2	— –
Number–Percentage	6 26%	6 24%	2 7%	– ——

n = Notched.

were infants. However, at the moment, we feel that there are no better criteria of right ventricular hypertrophy for either young or old individuals. We can be certain, at least, that all patients with such patterns had a defect which would logically invite right ventricular hypertrophy.

Cayler concludes that patients with an R of 20 mm. or greater in Lead V_1 *almost always* have systolic pressure in the right ventricle of at least 100 mm. Hg, and that, conversely, patients with an R of less than 20 mm. in Lead V_1 *rarely* have systolic pressure above 100 mm. Hg.

In our series, 5 of 58 patients with right ventricular pressure between 40 and 90 mm. Hg had an R in Lead V_1 of 20 to 26 mm. On the other hand, 22 of 36 patients with right ventricular pressure of 100 mm. Hg or more (highest, 150 mm.) had an R in Leads V_{3R} or V_1 of less than 20 mm. (range, 3 to 19 mm.). Although 92 per cent may allow "almost always," 61 per cent does not allow "rarely."

An explanation for the lack of correlation between the height of the R wave and the right ventricular pressure has been sought in our laboratory by Dr. Janet Dickens[6] by means of precordial and intracavitary electrocardiograms recorded simultaneously with pressure. No constant relationship between the parameters has been demonstrated.

Although we would like to establish criteria for the diagnosis of and severity of pure pulmonary stenosis on the basis of a study as universally accessible as electrocardiography, we find it impossible. The defect shares electrocardiographic patterns with other lesions which place a burden on the right ventricle. Although some mean measurements change in value with increasing degrees of stenosis and right ventricular hypertension, in an individual they cannot be accepted to reflect a certain degree of right ventricular hypertension.

SUMMARY

The electrocardiograms of 100 patients with pure pulmonary stenosis studied by right heart catheterization were reviewed.

For analysis, the subjects were grouped according to the systolic pressure in the right ventricle.

The majority of patients showed evidence of right ventricular hypertrophy, the frequency increasing with the severity of the stenosis. No diagnostic pattern was established.

The severity of the stenosis and the height of systolic pressure in the right ventricle cannot be gauged in the individual patient by the character of the tracing.

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Simultaneous Tachycardias

Agustin Castellanos, Jr., M.D., Luis Azan, M.D., and José M. Calviño, M.D.
Havana, Cuba

Although the first tracings of simultaneous independent tachycardias were published by Gallavardin,[1] in 1920, this arrhythmia did not attract general attention until 1952, when Bernstein and co-workers[8] reported 7 cases which they observed as occurring over a short period of time. These authors were of the opinion that the incidence of this disorder of rhythm was probably higher than that which was normally expected by electrocardiographers. Since we have also observed the presence of this arrhythmia in a proportionally large variety of records,[10] it was considered worth while to attempt to clarify the underlying mechanism as well as to describe the different forms.

MATERIAL AND METHODS

Our material consists of 15 cases studied from 1952 to 1958, in the Department of Cardiology at the University Hospital. Five of these cases were published previously.[10] This incidence is perhaps rather high and may be attributed to the use of additional esophageal leads which have been used as a routine procedure in 90 per cent of the patients observed to have ventricular tachycardias during the period from 1950 to 1955. Initially, the lead in which the P waves could best be seen was selected for study. Then, whenever long tracings were available, the differentiation between double tachycardias and the following arrhythmias was feasible: (1) Ventricular tachycardia with normal sinus rhythm which was due to the slow atrial rate and to the independence of the atrial from the ventricular complexes.[11] (2) Aberrant ventricular conduction of supraventricular beats, a phenomenon usually appearing when a somewhat premature and bizarre QRS complex followed a long R-R interval, with the complexes adopting, generally, the morphology of right bundle branch block. Furthermore, a definite relationship between the atrial and ventricular activity was found.[18] (3) Ventricular tachycardia with first or second degree retrograde block. In these cases a logical R-P sequence existed, consistent with the rules of V-A conduction, so that the irregularities of the P-P intervals when present could not be ascribed to irregular discharge of an ectopic center.[19] In this arrhythmia, as well as in the aberrant ventricular conduction, carotid pressure could affect the atrial rhythm and the A-V or V-A conduction time in such a way as to assure a definite relationship between atrial and ventricular activity. On the other hand, in all cases of simultaneous independent tachycardias the rapid atrial complexes showed no relationship whatsoever to the QRS complexes, and the P waves fell on various parts of the ventricular cycles. It is to be noted that the differentiation of ventricular tachycardia from A-V

From the Departments of Cardiology, Hospital Universitario and Hospital Clinico Quirurgico, Havana, Cuba.
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nodal tachycardia with aberration can seldom be made with absolute certainty unless fusion beats are present.[8,11] In all other instances the diagnosis of ventricular tachycardia is not intended to exclude the possibility of nodal tachycardia with aberrant ventricular conduction. Atrial fibrillation was excluded from this study. The initially present atrial tachycardias, as well as the A-V nodal tachycardia in Figs. 11, 12, and 13, originally had some degree of A-V block. Moreover, their production by digitalis was established after the use of short-acting preparations such as ouabain, strophanthidin, and acetyl strophanthidin on these patients. Following the injection of these drugs, a second pacemaker occurred, a finding which can be considered clearly deleterious and was not observed when the tachycardia was not due to digitalis.[32] Likewise, Figs. 8, 9, and 10 constitute examples of drug hypersensitivity, because an ectopic ventricular rhythm was seen without the disappearance of the initial nondigitalis-induced tachycardias. When drug overdosage was suspected, digitalization was performed according to the original method proposed by Lown and Levine,[21] and the amounts of digitalis administered were noted on the corresponding records. Only tracings with certain peculiarities will be presented.

RESULTS

Simultaneous Atrial and Ventricular Tachycardias (7 Cases).—The upper record of Fig. 1 shows an atrial tachycardia with a 2:1 A-V block produced by digitalis overdosage. The atrial rate varies from 200 to 250 per minute, due either to ventriculophasic arrhythmia or to an irregular discharge of the ectopic center.

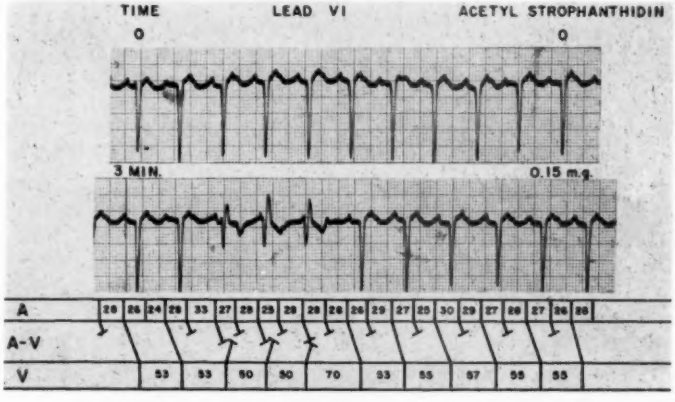

Fig. 1.—Simultaneous atrial and ventricular tachycardias. Diagrams are conventional.[22] All tracings in this figure, and in all others, are fully discussed in the text.

In the lower record, taken 3 minutes after the administration of 0.15 mg. of acetyl strophanthidin, the sixth P wave can be seen to become apparent 0.33 second after the preceding one, thus representing the longest P-P interval. Therefore, it furnished enough time for the appearance of an extrasystole, which would not have been present in the usual P-P sequence. This extrasystole, in turn, initiates a short run of tachycardia, and the resultant picture is one of an A-V dissociation in the presence of a 2:1 A-V block. As in all instances of this disorder of rhythm, the ventricular rate of 115 per minute, which is slower than the atrial rate of 214 to 275 per minute but is faster than twice the P-P interval of 109 to 111, persists until a QRS complex falls at the expected time. The same arrhythmia is present in the upper record of Fig. 2. In addition, multiple complexes of intermediate contour are observed as the result of obviously fusion

beats, so that the ventricular rhythm, doubtlessly, is not an A-V tachycardia with aberration. After a second injection of acetyl strophanthidin, the total amount now being 0.30 mg., the electrocardiographic image is that of simultaneous independent atrial and ventricular tachycardias (second and third strips). Finally, sinus rhythm is restored by the intravenous administration of potassium. This rhythm is interrupted by intermittent ventricular extrasystoles which have the same origin as the previously observed bizarre ventricular complexes.

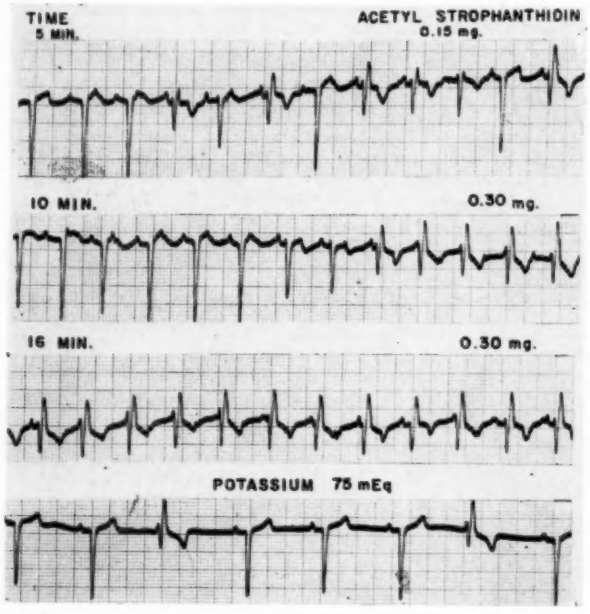

Fig. 2.—Simultaneous independent atrial and ventricular tachycardias.

Electrocardiograms similar to the preceding one in which the onset of a double rhythm can be observed have been published by Katz and Pick (Fig. 214)[11] and by Dressler and Roessler (Fig. 4).[9] In every instance it has been clear that the ventricular center was "active," that is, with its own automatism and evidently not by a succession of escapes (passive rhythm) as frequently happens when sinus rhythm is the underlying atrial mechanism accompanying dissociation with interference in 2:1 A-V block.

Simultaneous Atrial and Bidirectional Ventricular Tachycardias (3 Cases).— In the upper strip of Fig. 3 an atrial tachycardia with a rate of 150 per minute with irregular A-V block can be seen; it is obviously due to digitalis overdosage. The middle strip, taken after acetyl strophanthidin was administered, shows the onset of a bidirectional ventricular tachycardia which succeeds a normally conducted beat labeled "N." Finally, the bottom strip showing esophageal leads, obtained a few minutes later, reveals the independence of the atrial from the ventricular complexes, establishing the diagnosis of double tachycardias. The atrial rate has increased to 187 per minute, but the ventricular tachycardia remains unchanged.

The effects of intravenous procaine amide are presented in Fig. 4. The ventricular tachycardia has disappeared after the administration of only 300 mg. of procaine amide (shown in the upper tracing taken 30 minutes after starting the test). The atrial rhythm has decreased to 165 per minute but is still an atrial

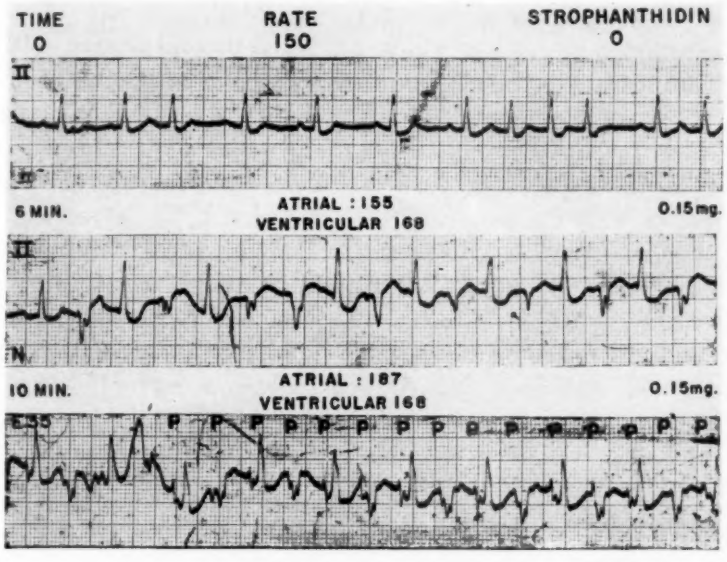

Fig. 3.—Simultaneous independent atrial and bidirectional ventricular tachycardias.

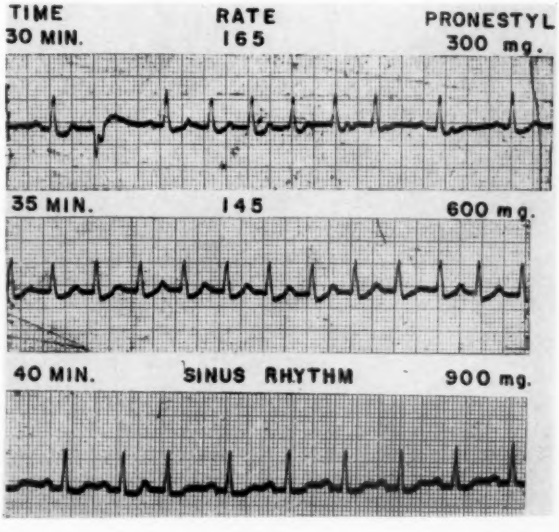

Fig. 4.—The effects of procaine amide on the double tachycardias of Fig. 3.

tachycardia with varying A-V conduction. Moreover, as a consequence of the administration of 600 mg. of procaine amide, as indicated in the middle tracing, a further reduction in the rate to 145 per minute can be seen with the establishment of 1:1 A-V conduction with prolonged A-V conduction time (0.20 second).

In the lower tracing, sinus rhythm is again present after the injection of 900 mg. of procaine amide. The third ventricular complex corresponds to a premature atrial systole, probably arising from the same focus as the tachycardia.

An arrhythmia similar to that described in the preceding paragraph is illustrated in Fig. 5. A careful analysis of the upper strip reveals the existence of an atrial tachycardia with a prolonged P-R interval (0.20 second), corroborated by carotid pressure, a maneuver which produced second degree A-V block (not shown). Five minutes after acetyl strophanthidin was injected, a bidirectional ventricular tachycardia appeared, coexistent with the atrial tachycardia shown in the middle strip. However, the correct diagnosis was established only after the recording of the esophageal leads. Paradoxically, a decrease in the atrial rate, as compared with control values, is evident in the latter, combined with an irregular spacing of nearly all P-P intervals. Yet, the P waves are not related to the QRS complexes, the rate of these still being 170 per minute. Hence, the exact electrocardiographic interpretation is double tachycardias, one originating in the atria and the other, bidirectional, in the ventricles. Two similar cases have been reported by Luten (Fig. 6[3]; Fig. 8[4]).

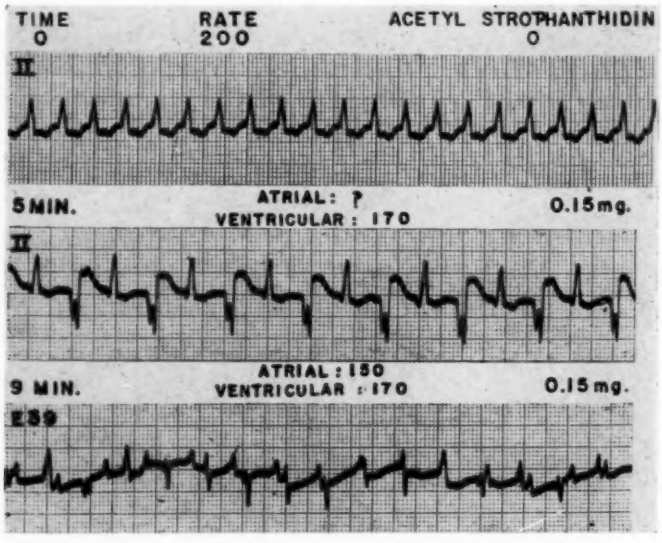

Fig. 5.—Simultaneous independent atrial and bidirectional ventricular tachycardias.

Simultaneous Atrial and A-V Nodal Tachycardia (1 Case).—Figs. 6 and 7 are examples of how double tachycardias were produced during digitalization in a 9-year-old girl with rheumatic fever. The top tracing in Fig. 6 shows a sinus tachycardia with a rate of 123 per minute before the administration of oral digoxin, 2 mg. in two doses 8 hours apart. In the other strips, Leads I and II, an atrial tachycardia with first degree A-V block is present with a rate of 145 per minute, with all P waves having a different morphology than the slightly slower sinus ones. Occasionally, an interesting form of alternation appears in which a short R-R is preceded by a longer R-R. Because interatrial timing is constant, the mechanism must be considered to be a form of alternation of A-V

conduction, a term introduced by Langendorf.[20] Indeed, it can be appreciated that the shorter P-R intervals follow the shorter R-P intervals and, vice versa, the longer P-R intervals follow the longer R-P intervals (all values marked on the bottom tracing are expressed in hundredths of a second). This suggests a supernormal phase of A-V conduction. Unfortunately, the attending physician administered an additional 0.5 mg. of digoxin because of what he interpreted on the basis of auscultation as only an increase in the sinus rate. The resultant

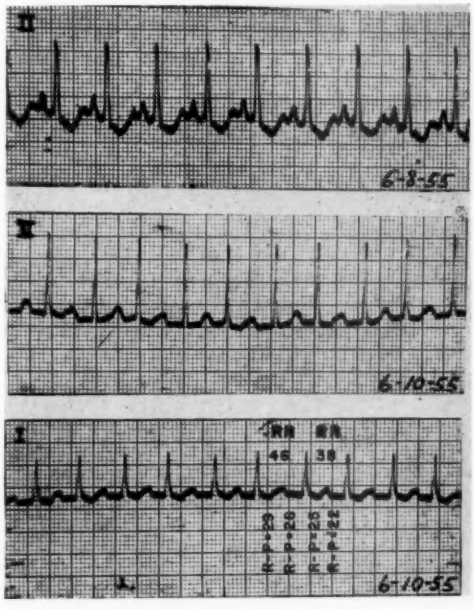

Fig. 6.—Sinus tachycardia (upper strip); first degree auriculoventricular block with alternation of A-V conduction time due to the supernormal phase (lower strips).

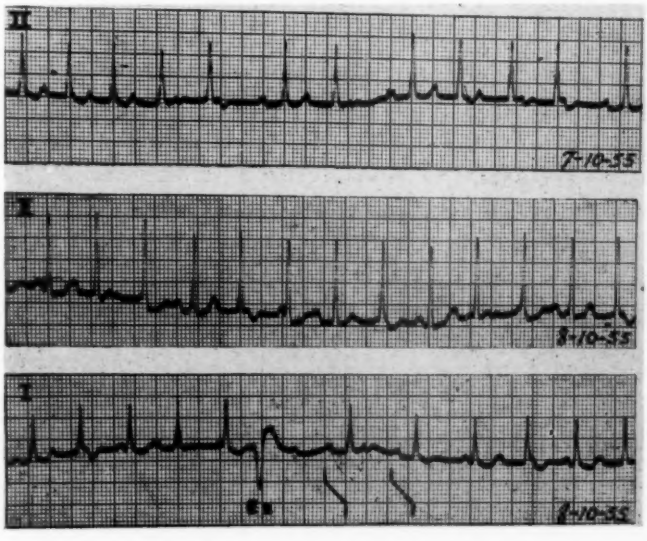

Fig. 7.—Atrial tachycardia with auriculoventricular block (upper strip); simultaneous atrial and A-V nodal tachycardias (lower strips).

picture, which is presented in the strip labeled *7-10-55* in Fig. 7, is that of an atrial tachycardia with the irregular A-V block having approximately the same rate as before. One day later, 8-10-55, in spite of no further digitalization an A-V tachycardia appeared with a rate of 133 per minute, coexisting with atrial arrhythmia, the rate of the latter having increased to 170 per minute. Thus, simultaneous dissociated action of both pacemakers is present. In the lower strip a curious phenomenon is noted when a ventricular extrasystole is retrogradely conducted to the A-V center, suppressing it. Since the effect is revealed by the unexpected failure of the pacemaker to appear when expected, it can be considered as an example of concealed retrograde conduction as conceived by Langendorf.[22]

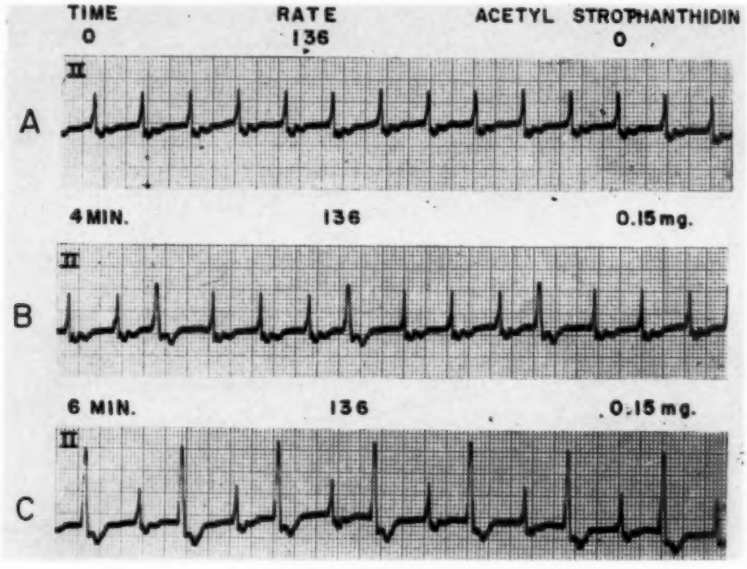

Fig. 8.—A-V nodal tachycardia with ventricular extrasystoles.

Understandably, the oncoming atrial impulse, P_1, cannot activate the ventricles, but by the time P_2 reaches the A-V junction, transmission could have been possible. Because this impulse is also blocked, it has to be accepted that an unusually prolonged state of A-V refractoriness is the cause for such stoppage. The succeeding P wave, P_3, is conducted to the ventricles because of the depression of the A-V center at a time when A-V conduction was feasible.[23] Thereafter, P_4 is blocked and P_5 is conducted. The nodal center then "warms up" and the A-V tachycardia starts anew, so that again two completely independent tachycardias are simultaneously present.

Simultaneous A-V Nodal and Ventricular Tachycardias (3 Cases).—The tracings shown in Fig. 8 were recorded on a patient with encephalomyocarditis who definitely had received no digitalis previously. Tracing *A* reveals an A-V nodal tachycardia with a rate of 136 per minute, with retrograde stimulation of the atria which is not due to digitalis. In tracing *B* an initial injection of acetyl strophanthidin produced intermittent ventricular extrasystoles with a very long coupling. Precisely, it is due to such a long coupling that their retrograde

conduction reached the A-V center after it had already discharged toward the atria (all P-P intervals are identical), thus creating an impedance to transmission of the nodal beats toward the ventricles. Finally, in tracing *C* the same late extrasystoles are seen after each nodal beat and represent a true bigeminy.

The tracing in Fig. 9 was obtained 24 hours later from the same patient as in Fig. 8, after the administration of 0.15 mg. of acetyl strophanthidin. The fourth QRS complex is, beyond doubt, a ventricular extrasystole, which, in turn, initiates a run of bidirectional ventricular tachycardia with all beats having retrograde conduction to the atria, as revealed in the diagram. Consequently, because the A-V center was reached and suppressed, a double tachycardia did not exist.

Twenty-four hours later the patient under consideration received an injection of 0.10 mg. of ouabain (Fig. 10). The basic rhythm was now an A-V nodal tachycardia with preceding activation of the atria (first and last three beats). Again an ectopic (second) QRS complex initiated a run of bidirectional ventricular tachycardia. However, on this occasion, plotting the P-P intervals revealed no change in atrial activation. For this reason it must be accepted that the retrograde conduction of the extrasystole did not reach the A-V center, so that the rhythmical activity to the atria was uninterrupted yet causing impedance to the transmission to the ventricles. Consequently, it is clear that two simultaneous tachycardias existed side by side, one originating in the upper region of the A-V junction and the other, bidirectional, in the ventricles.

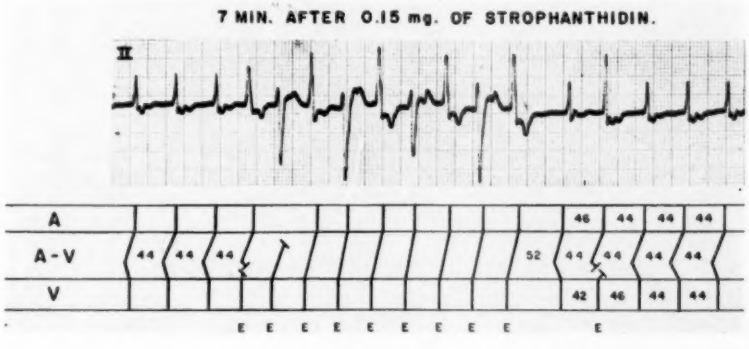

Fig. 9.—A-V nodal tachycardia interrupted by a short run of bidirectional ventricular tachycardia.

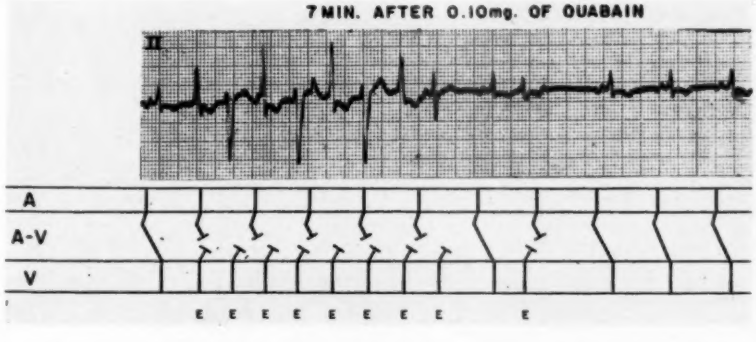

Fig. 10.—Simultaneous independent A-V nodal and bidirectional ventricular tachycardias.

Another example of this arrhythmia is presented in Figs. 11, 12, and 13. Initially, the upper record of Fig. 11 shows a sinus rhythm with a rate of 97 per minute, which changes, toward the middle of the tracing, into an apparently passive A-V rhythm with a rate of 79 per minute, with first degree A-V block and a P-R interval of 0.12 second. This patient had been receiving 0.25 mg. of digoxin daily for the previous months, without any sign of intolerance. Yet 1 week later when the dose was abruptly increased to 1.5 mg. because of unequivocal signs of congestive heart failure, a nonparoxysmal A-V tachycardia with a rate of 136 per minute appeared, and is seen in the lower strip. Note that the P-R interval was still 0.12 second. Because some observers had serious doubts whether the tachycardia was drug induced or simply a spontaneous arrhythmia appearing during an episode of congestive failure, a test of digitalis tolerance was carried out. In tracing *A* of Fig. 12 the atrial rate shows an increase to 167 per minute after 0.20 mg. of strophanthidin, and a ventricular tachycardia becomes evident. The rate of the latter was originally 140 per minute, but as the pacemaker "warmed up," it increased to 172 at the end of the tracing. Yet, both pacemakers are completely independent, the record showing the presence of simultaneous A-V and ventricular tachycardia.

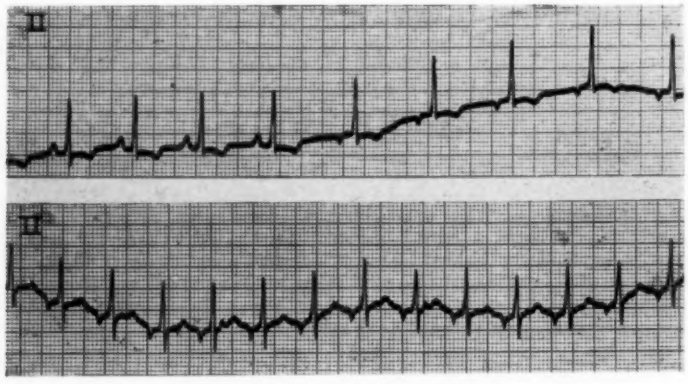

Fig. 11.—Sinus rhythm changing into A-V nodal rhythm (upper strip); nonparoxysmal A-V nodal tachycardia (lower strip).

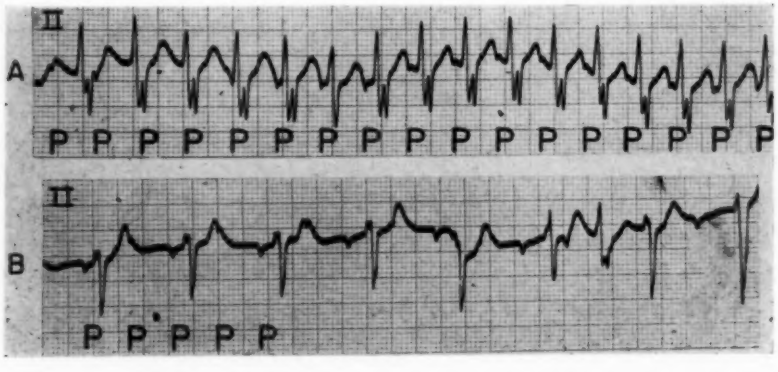

Fig. 12.—*A*, Simultaneous independent A-V nodal and ventricular tachycardias. *B*, Simultaneous independent A-V nodal and ventricular tachycardias, the latter with 2:1 exit block.

In tracing *B* of Fig. 12 a ventricular rhythm is seen dissociated from the A-V center. All inverted P waves fall in various parts of the R-R cycle, and the fact that the ventricular rate of 86 per minute is exactly half of that of the tachycardia which occurred at the end of *B* is noteworthy. Evidently, in this case the assumption of a ventricular tachycardia with a 2:1 exit block is justified and, furthermore, corroborated by the finding of a QRS complex occurring midway from the sixth and eighth ventricular deflections. The similarity of this complex with those in tracing *B* is to be noted, and its slight widening is probably due to a more sinuous spread of activation through the ventricles when the pacemakers speeded up and can be explained by a transient disappearance of the exit block. The resultant picture is that of simultaneous independent A-V nodal and ventricular tachycardias, the latter with a 2:1 exit block.

The phenomenon presented in Fig. 13 took place in spite of no further digitalization (*B*, *C*, and *D* are continuous). In tracing *A*, recorded 2 minutes after the preceding Fig. 12, the A-V nodal tachycardia persists at the usual rate, but now an additional, moderately rapid ventricular rhythm, independent of the nodal rhythm, can be seen. The QRS complexes are wider and have a dif-

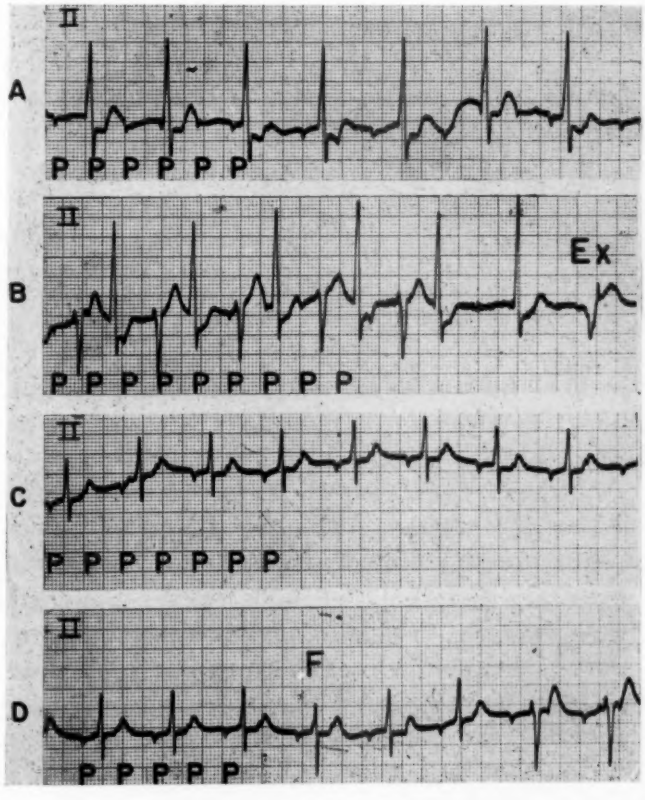

Fig. 13.—*A*, Simultaneous independent A-V nodal and ventricular tachycardias. *B*, Simultaneous independent A-V nodal and ventricular tachycardias, the latter possibly having varying exit block as well as irregular intraventricular propagation. *C*, A-V nodal tachycardia with 2:1 exit block. *D*, Transition to dissociation with interference due to the reappearance of the ventricular tachycardia with 2:1 exit block.

ferent morphology than those observed in the lower strip of Fig. 12. Consequently, a different origin can be postulated, but one pacemaker may be operating on both occasions yet with different propagation through the ventricles. Both types of complexes are alternatively present in tracing *B*, whereas the A-V nodal tachycardia remains undisturbed so that the electrocardiographic image is that of a bidirectional ventricular tachycardia. Its spontaneous transient disappearance can be observed toward the end of the tracing. First, the downward directed complexes vanish, but the upward directed ones persist until their suppression by a ventricular extrasystole. The possibility of two independent ventricular rhythms can also be considered in this record, making a total of three simultaneous tachycardias, although a single ventricular pacemaker with varying exit block and alternation in its propagation through the ventricles is more likely.

These difficulties apply to the understanding of all theories which try to explain the genesis of bidirectional tachycardias (Fig. 215[11]). However, in this particular case a supraventricular origin can be ruled out because of the finding of fusion beats (see below). Next, *C*, continuous with *B*, shows that after the extrasystole the nodal tachycardia has reappeared, now having a second degree A-V block. Finally, this type of conduction persists until the ectopic downward ventricular complexes are again observed in *D*, so that both pacemakers are unquestionably dissociated. The presence of a fusion beat (*F*) assures the ventricular origin of the lower rhythm. Consequently, A-V nodal tachycardia with aberration can be discarded, and an upper A-V nodal tachycardia coexists with a ventricular tachycardia. Thus, the diagnosis in this last part of *D* is dissociation with interference in a 2:1 A-V block.

Simultaneous Independent A-V Tachycardias (1 Case).—The only published example of this arrhythmia was reported in a recent communication from our department.[17]

COMMENT

One of the most controversial points concerning double tachycardias is whether atrial impulses are stopped at the A-V junction by the normal or by an abnormally prolonged refractoriness (true block) provoked in the latter tissues by the lower pacemakers. Whenever the rate of the lower center is rapid enough, it is conceivable that the impulses reach the intermediate tissues in such rapid succession that they are kept in a permanent state of normal refractoriness.[11]

However, from the examples presented in this communication it was evident that prior to the appearance of the lower pacemaker an atrial or a nodal (Fig. 11) tachycardia with A-V conduction disturbances existed. The belief that the mechanism was a true block was suggested by the following findings: (1) the disorder of rhythm was digitalis induced, except in Fig. 8, and (2) the atrial rate by itself was occasionally too slow to account for the abnormal A-V conduction, Figs. 3 and 4 (see Reference 11, Figs. 173 and 174). Also, as in Fig. 1, when the beginning of a ventricular tachycardia occurring during an ectopic rapid atrial rhythm was recorded by other authors, some degree of A-V block was clearly shown (see Fig. 214 of Reference 11, and Fig. 4 of Reference 9).

In conclusion, enough evidence has been accumulated so that it can be assumed that, certainly, in a great number of cases of double tachycardia some degree of impedance to A-V conduction is present but a complete A-V block does not exist, however. The incidence of the arrhythmia under consideration is possibly greater than one is led to believe in view of the few published electrocardiograms. For instance, in support of this argument it can be stated that Bernstein and his associates[8] reported 7 cases in a 10-month period. Perhaps in one or two of his tracings, coarse atrial fibrillation could have been the supraventricular rhythm. In our previous studies on double tachycardias, as well as in Figs. 3 and 5 of the present report, the correct interpretation would have been impossible except for the use of esophageal leads. During the period 1952 to 1955, we employed esophageal leads routinely in about 90 per cent of our cases of ventricular tachycardia. For this reason our incidence of double tachycardias is probably higher than in a series in which only the conventional twelve leads are recorded.

A detailed analysis of case histories revealed that the disorder of rhythm was digitalis induced except in one patient (Figs. 8, 9, and 10). Even in that case it was clearly shown that the drug, although not responsible for the nodal tachycardia, indeed produced the bidirectional ventricular tachycardia. In contrast, only 58 per cent of Bernstein's cases had that origin. However, a review of the literature since the original experiences of Luten in 1925, reveals that digitalis played an important role in over 75 per cent of the cases on which required data were included (Table I).

Throughout Figs. 1 to 12, we presented the sequence in which the arrhythmia appeared. First, the atrial tachycardia appeared, followed by the nodal or ventricular tachycardia, the former in a nonparoxysmal form and the last two in either a paroxysmal or in a nonparoxysmal form. Also, it is to be noted in Figs. 1 to 10 that the lower rhythm was produced by progressive increments of intravenous digitalis drugs. In spite of acetyl strophanthidin being considered extremely toxic, our experience led us to believe that its effects were similar to those of strophanthidin or ouabain. This is well illustrated in Figs. 8, 9, and 10, in which a similar arrhythmia was produced on three different occasions by three different drugs.

Nevertheless, some factors must be kept in mind when interpreting the test of digitalis tolerance, for there is reason to believe that an increasingly grave electrocardiographic picture due to the appearance of ventricular ectopic rhythms does not necessarily indicate that the pre-existing tachycardia was due to digitalis excess. In some rare cases, hypersensitivity may be the cause of these alterations. For instance, Figs. 8, 9, and 10 show how minor amounts of intravenous preparations produced a toxic response in a patient whose basic rhythm was an A-V nodal tachycardia which was definitely spontaneous. A thorough study of the case history revealed positively that digitalis had not been administered previously. Accordingly, we had to accept the fact that toxic effects became evident before the therapeutic effects were achieved (considered as the abolition of the A-V tachycardia).

Therefore, it has to be admitted that hypersensitivity may lead the observer to believe that large doses of digitalis have been administered previously, when such is not so. Yet, such findings are infrequent and, as a rule, the therapeutic implications will be the same in each instance, namely, that further digitalization is contraindicated. On the other hand, in nearly all instances of atrial tachycardia with first degree A-V block due to digitalis poisoning (except in Fig. 5) a second degree block was induced before the beginning of the lower tachycardia. It is to be seen that in Figs. 11, 12, and 13 such a block appeared after the end of the ventricular tachycardia. In these rhythms a toxic effect was definitely the only possibility because no therapeutic results were to be expected. A drug-induced toxic rhythm could not be abolished by the same drug which induced the arrhythmia. This finding is in contrast with what occurs when one is dealing with spontaneous atrial tachycardias, because in this case the abolition or no modification of the abnormal rhythm is the rule after digitalization.[32]

Invariably, the prognosis of double tachycardias is poor, not solely on account of the arrhythmia but because it usually exists in patients with a badly damaged myocardium. The great majority of the individuals in this study were elderly

TABLE I. SUMMARY OF THE REPORTED CASES OF DOUBLE TACHYCARDIAS

	CASES	YEAR	DIGITALIS
Atrial* and Ventricular Tachycardias:			
Gallavardin[1]	1	1920	Yes
Barker[2]	1	1924	Yes
Luten[3,4]	3	1925	Yes
McMillan and Bellet[5]	2	1932	?
Stern[6]	1	1937	?
Kayden, et al.[7]	1	1951	No
Bernstein, et al.[8]	6	1952	Yes (3 cases)
Dressler and Roessler[9]	1	1952	Yes
Calviño, et al.[10]	5	1955	Yes (5 cases)
Katz and Pick[11]	1	1956	Yes
Miller and Scharett[12]	1	1957	?
Anderson and Rubin[31]	1	1958	Yes
Atrial* and A-V Nodal Tachycardias:			
Luten[4]	1	1925	Yes
Howard[13]	1	1927	Yes
Schott[14]	1	1946	?
Bernstein, et al.[8]	1	1952	Yes
Calviño, et al.[10]	1	1955	Yes
Katz and Pick[11]	1	1956	?
Shmagranoff and Jick[15]	1	1957	Yes
Calviño, et al.[16]	1	1957	Yes
Marriott, et al.[29]	1	1958	?
A-V Nodal and Ventricular Tachycardias:			
Miller and Scharett[12]	1	1957	?
Simultaneous A-V Tachycardias:			
Castellanos, et al.[17]	1	1958	Yes
Simultaneous Ventricular Tachycardias:			
No case has been reported			

*Atrial flutter included.

patients with arteriosclerotic heart disease and refractory heart failure. The only exception was a 9-year-old girl with rheumatic fever (Figs. 6 and 7), which to our knowledge is the only published case of this arrhythmia in children. It is true that in many patients, death has been caused by the ectopic rapid rhythm, which can lead to ventricular fibrillation. Yet all deaths should not necessarily be attributed to this cause, because poor myocardial function with refractory heart failure can, in all probability, be responsible. For example, the patients whose tracings are presented in Figs. 6 and 10 died several days after sinus rhythm was re-established by appropriate treatment.

When short-acting digitalis preparations produced the arrhythmias, they were treated either with procaine amide or potassium. Both drugs had a similar effect, detected whenever long tracings were obtained. Initially, the ventricular tachycardia disappeared, and then the pre-existing atrial tachycardia with irregular A-V conduction was again observed. Thereafter, 1:1 A-V conduction accompanied by a progressive decrease in rate and P-R interval was seen until the return of sinus rhythm. The shortening of the P-R interval is a paradoxical finding, for it is known that toxic doses of Pronestyl prolong A-V conduction time.[25] Because of this behavior the similarity between atrial tachycardia with block and experimental tachycardias produced by electrical stimulation was stressed in a previous communication.[26] Furthermore, one case of atrial tachycardia associated with digitalis administration with a 2:1 exit block has been reported, a phenomenon which is a property of automatic rhythms.[16]

In view of the foregoing arguments, it is possible that atrial tachycardias produced by digitalis can be due to an automatic center in the atria. Then perhaps it can be more than a coincidence that a case of double tachycardias has been published in which the ventricular rhythm was parasystolic (automatic) (Reference 11, Fig. 214).

Another interesting finding evident in Figs. 1, 2, and 5 was a marked irregularity of the P-P intervals during atrial tachycardias. Careful analysis revealed that they were not due solely to ventriculophasic arrhythmia and could be explained on the basis of an irregular discharge of a single pacemaker. This possibility was postulated in clinical cases by Katz and Pick[11] (page 284) and positively demonstrated in the laboratory by Scherf and associates.[27] Moreover, in the latter experiments it was shown how aconitine-induced atrial tachycardias could respond dually to vagal stimulation. This maneuver could slow as well as increase the rate of the automatic center. Also, an irregular spacing of the P-P interatrial intervals could be seen in their tracings. A similar dualistic behavior can be noticed in the original experiments of Lewis.[28]

These findings have a counterpart in some of the cases of atrial tachycardias due to digitalis toxicity presented in this communication. For instance, when this drug was administered, an increase in rate usually ensued (Fig. 3), but no change (Figs. 1 and 2) as well as a decrease have also been observed (Fig. 5). Such a different effect on atrial rate can be explained on the basis of the vagal action of digitalis.

SUMMARY

Various combinations of simultaneous tachycardias have been observed to occur in the human heart. As a rule, the coexisting atrial and ventricular forms are the most frequent. When esophageal leads were used, the incidence of these arrhythmias was found to be greater than that reported by other authors. This greater incidence was due to the fact that without esophageal leads the atrial rhythm in many cases could not be interpreted correctly because the widened QRS complexes sometimes obscured the atrial deflections. Digitalis was the cause of these arrhythmias in over 75 per cent of the cases studied. This was well demonstrated in cases in which the double rhythms were induced by the intravenous administration of short-acting digitalis preparations. Appropriate treatment with potassium and procaine amide usually abolished the tachycardias promptly. Contrary to the usual belief, the prognosis was not necessarily dependent upon the nature of the disorder of the rhythm but chiefly upon the precarious conditions of the myocardium. As a rule, these arrhythmias were most frequently seen in elderly patients with arteriosclerotic heart disease.

A single exception was that of simultaneous tachycardias occurring in a 9-year-old girl with rheumatic fever who died several days after sinus rhythm was restored. Whenever the rate of the lower pacemaker was rapid enough, it was conceivable that the atrial impulses could not transverse the A-V junction because of the refractoriness provoked in the latter by the lower pacemaker. However, it was demonstrated that some degree of abnormal refractoriness or true block was present. Yet, obviously, a complete A-V block did not exist. This impedance to conduction was ascribed mainly to the toxic effects of digitalis.

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A Quantitative Study of Initial and Terminal QRS Vectors in a Group of Normal Older Men

Hiroyoshi Mori, M.D., Kyoichi Nakagawa, M.D.,** James C. Dahl, M.D., Otto H. Schmitt, Ph.D., and Ernst Simonson, M.D.,*** Minneapolis, Minn.*

INTRODUCTION

The clinical importance of the initial and terminal vectors of the QRS complex has been recognized for many years. The importance of the initial QRS vectors in myocardial infarction, and of the terminal QRS vectors in bundle branch block has been well established. These data are, however, essentially qualitative, and, in general, in the vectorcardiographic literature the analysis is limited to an inspection of loop projections in the horizontal, frontal, and sagittal planes.

Pipberger[1] recently has quantitated initial QRS vectors in a group of 70 normal subjects.

The purpose of this study is to present quantitative normal standards for the initial and terminal QRS vectors in a group of older men. These vector quantities were derived from simultaneously recorded scalar electrocardiograms using the SVEC-III orthogonal system devised by Schmitt,[2] and are presented in readily interpretable spatial polar coordinates (azimuth, elevation) rather than in terms of projections of spatial vectors on the horizontal or sagittal plane. The calculations have been based on the Cartesian scalar components, however, because the initial and terminal time segments are read only with the greatest difficulty in spatial or planar loops.

MATERIAL AND METHOD

The subjects studied were 93 men all in their sixth decade of life. These men were a portion of a larger group of men who have been studied annually in the Laboratory of Physiological Hygiene for the past 12 years. None of the individuals included in this study had manifested

From the Laboratory of Physiological Hygiene, and the Department of Biophysics, University of Minnesota, Minneapolis, Minn.

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*Present address: Tokushima University Medical School, Tokushima-City, Japan.
**Present address: Nagoya University Medical School, Nagoya-City, Japan.
***Requests for reprints should be addressed to Dr. Ernst Simonson, Laboratory of Physiological Hygiene, Stadium Gate 27, University of Minnesota, Minneapolis 14, Minn.

clinical or laboratory evidence of cardiovascular disease at any time during the period of observation. Serial studies included: detailed medical histories, physical examinations, chest x-rays, biochemical determinations, standard electrocardiograms, and a variety of stress tests.

A standard 12-lead electrocardiogram and a scalar 3-lead electrocardiogram representing the X, Y, and Z axes were recorded with a four-channel Sanborn instrument, a fourth time-reference lead being included in each set of records in order to permit accurate time cross reference. A special preprogrammable switch system was utilized to make possible instant choice of any of four chosen groups of 4 leads. A paper speed of 100 mm. per second and a fine-line heat stylus were used for the recording, in order to permit easy, accurate measurements of the short time intervals involved in the initial and terminal vectors. The X, Y, and Z leads of the SVEC-III system were shown in model experiments to have less distortion than twelve other lead systems compared.[2]

The amplitude of the QRS complex at 10, 20, 30, and 40 milliseconds from the earliest starting point and retrograde from the extrapolated terminal foot-point was measured with the aid of a magnifying lens. It will be noted that on this time scale the dynamic response of the Sanborn writer is not quick enough to make residual errors in the measurements entirely negligible, but this error is here treated as a systematic one and is not individually corrected. In order to evaluate the significance of this error in dynamic response, ventricular complexes were simultaneously recorded in one lead of the Sanborn recorder and in an oscilloscope at speeds of 25, 50, and 100 mm. per second. The oscilloscopic trace was photographed. There was no measurable difference in the QRS durations noted at any of the three recorded speeds. It is concluded that although a significant lag does occur with the Sanborn recorder when a sine or square-wave input signal is recorded at 10 cycles per second at speeds used in these experiments, the initial and terminal starting points for measurement can be accurately obtained, and comparative measurements are therefore valid.

The extrapolated "earliest appearing starting point" and the latest appearing foot-point in any of the three simultaneously recorded QRS complex components were designated, respectively, as the initial and terminal points. The determination of initial and terminal points in those complexes in which the starting or terminal points were not clearly seen, and formed a concave arc, was carried out in the following manner: the initial or terminal starting points were taken at the intercept of straight lines parallel to the respective upstroke or downstroke of the QRS complex and the base line.

Translation from the scalar amplitude values in the X, Y, and Z components to the spatial polar forms of the initial and terminal vectors was accomplished with the aid of a mechanical spatial vector analyzer.[3] These values are expressed as azimuth, elevation, and magnitude of the vectors.

In this analysis the subjects were subdivided according to duration of the QRS complex and the electrical position of the heart. The subjects classified in the group with a wide QRS had a QRS interval greater than 100 msec., and those in the group with a narrow QRS had a QRS duration of less than 90 msec. The subjects were also divided into three positional groups according to the elevation of the QRS maximum: horizontal, 0 to -90 degrees; intermediate, 0 to $+60$ degrees; and vertical, $> +60$ degrees. These groups were selected by determination of the mean frontal plane QRS axis.

The angular velocity (magnitude) of the voltage vector sweep is determined from the spatial angle between successive initial and terminal vectors. The sweep speed of the voltage vectors is defined as the vector differences between successive voltage vectors divided by the time interval between them, and is calculated using the formula $\sqrt{a(\text{Sin } a)^2 + b(\text{Cos } a)^2}$, where a is the magnitude of the first vector and b is the magnitude of the succeeding vector. Alternatively, it may be measured directly using the vector analyzer.

RESULTS

The mean values and standard deviations of the azimuth, elevation, and magnitude of each initial and terminal 10, 20, 30, and 40 msec. are tabulated in Table I. These data are graphically presented in Fig. 1. Referred to the subject, the initial 10-msec. vector is directed to the right, forward and upward, the

mean azimuth being 115 degrees, and the elevation being 94.1 degrees. The 20, 30 and 40-msec. vectors are vectors directed anteriorly, inferiorly and to the left, with increasing magnitude and leftward projection of each instantaneous vector.

TABLE I. MEAN VALUES AND STANDARD DEVIATIONS OF AZIMUTH, ELEVATION, AND MAGNITUDE OF EACH INITIAL AND TERMINAL 10, 20, 30, AND 40-MSEC. VECTOR

			AZIMUTH	ELEVATION	MAGNITUDE
Initial Vector	0.01″	Mean	+115.0	94.1	1.141
		S.D.	31.2	24.3	1.562
	0.02″	Mean	+71.1	82.3	2.918
		S.D.	31.9	15.6	1.381
	0.03″	Mean	+26.0	73.6	6.965
		S.D.	23.4	10.6	2.507
	0.04″	Mean	−2.0	67.2	10.205
		S.D.	24.2	13.6	2.804
Terminal Vector	−0.01″	Mean	−106.8	94.3	1.325
		S.D.	31.6	38.8	0.794
	−0.02″	Mean	−101.6	96.0	3.259
		S.D.	25.3	25.2	1.493
	−0.03″	Mean	−93.4	90.7	5.567
		S.D.	30.7	20.7	2.372
	−0.04″	Mean	−67.9	78.4	7.413
		S.D.	40.4	20.4	3.105

TABLE II. RATIO OF THE MAGNITUDE OF THE MEAN QRS VECTOR TO EACH INITIAL AND TERMINAL VECTOR, AND SPATIAL ANGLES BETWEEN MEAN QRS AXIS AND EACH INITIAL AND TERMINAL VECTOR IN 93 NORMAL OLDER MEN

	INITIAL VECTOR	TERMINAL VECTOR
Ratio:		
0.01″/Mean	0.111	0.129
0.02″/Mean	0.285	0.318
0.03″/Mean	0.679	0.543
0.04″/Mean	0.995	0.723
Angle:		
0.01″	131	88
0.02″	78	86
0.03″	39	77
0.04″	17	42

The mean azimuth for the 40-msec. vector was −2 degrees, and the elevation was 67.2 degrees. The terminal vectors show a progressive counterclockwise rotation as viewed from above with rapidly decreasing magnitude.

The graphic representation of these vectors shows the angular velocity of the initial vectors to be greater than that of the terminal vectors.

Table II shows the fractional magnitudes of each initial and terminal vector in terms of the mean QRS-vector magnitude. These data indicate that the initial 40-msec. vector is practically as large as the mean QRS vector. The angle between these two vectors (17 degrees) is also small.

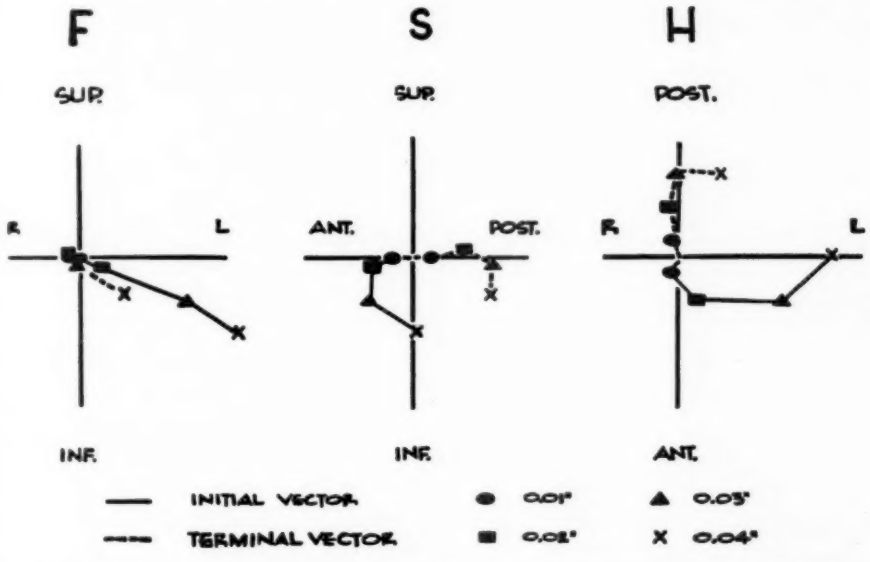

Fig. 1.—Total group. Vectorcardiograms constructed from the mean values of the amplitudes of the X, Y, and Z scalar leads of the SVEC-III system in 93 normal older men. *F* = frontal plane, *S* = sagittal plane, and *H* = horizontal plane.

TABLE III. ANGULAR SPEED (DEGREES/10 MSEC., UPPER PART) AND LINEAR SPEED (DISTANCE BETWEEN VECTOR END POINTS/10 MSEC.) IN THE SUCCESSIVE SEGMENTS OF INITIAL AND TERMINAL VECTORS. MEANS OF 93 OLDER MEN

	INITIAL VECTOR	TERMINAL VECTOR
0.01″ and 0.02″	52	8
0.02″ and 0.03″	41	14
0.03″ and 0.04″	27	36
0″—0.01″	1.14	1.33
0.01″—0.02″	2.39	1.96
0.02″—0.03″	5.13	2.53
0.03″—0.04″	5.12	4.38

The angular and linear speed between successive initial and terminal vectors is represented as an average figure of the group in Table III. These data show clearly the rapid initial rotation and the subsequent retardation in the terminal phase.

Because the calculated linear speed is a function not only of the magnitude of the instantaneous vectors but of the angle α as well, the linear speed increases between 20 and 40 msec. even though the angular velocity progressively decreases.

TABLE IV. MEAN VALUES AND STANDARD DEVIATIONS OF AZIMUTH, ELEVATION, AND MAGNITUDE OF EACH INITIAL AND TERMINAL VECTOR IN WIDE AND NARROW QRS GROUPS

			WIDE QRS GROUP			NARROW QRS GROUP		
			AZIMUTH	ELEVATION	MAGNITUDE	AZIMUTH	ELEVATION	MAGNITUDE
Initial Vector	0.01″	Mean	+116.7	97.5	0.945	+105.4	93.9	1.324
		S.D.	27.8	23.2	0.531	34.4	22.5	0.563
	0.02″	Mean	+77.0	81.1	2.477	+60.3	83.6	3.579
		S.D.	28.6	14.3	0.987	34.3	15.3	1.528
	0.03″	Mean	+35.0	72.1	6.090	+17.4	73.3	8.330
		S.D.	20.5	10.4	2.144	25.5	11.3	2.678
	0.04″	Mean	+5.7	66.9	9.939	−9.9	65.9	10.527
		S.D.	19.6	11.9	2.651	25.7	17.2	3.367
Terminal Vector	0.01″	Mean	−114.4	98.4	0.794	−104.5	96.2	1.809
		S.D.	34.2	44.2	0.366	32.7	39.8	0.913
	0.02″	Mean	−108.3	99.8	2.152	−97.6	95.2	4.176
		S.D.	29.8	26.1	0.665	26.8	28.3	1.760
	0.03″	Mean	−104.3	98.6	4.235	−80.2	86.0	6.924
		S.D.	21.6	17.6	1.358	41.9	22.1	2.998
	0.04″	Mean	−92.5	88.6	5.894	−45.0	68.7	8.997
		S.D.	24.6	17.4	2.062	41.3	20.7	3.830

The influence of the total QRS duration on the direction, magnitude, and angular speed of initial and terminal vectors was analyzed. Table IV shows the mean values and standard deviations of the azimuth, elevation, and magnitude of the initial and terminal QRS vectors in the group with narrow, and that with wide, QRS duration. The differences noted were further analyzed for significance by the t-test and are tabulated in Table V. There were significant differences in direction and magnitude of the vectors for these two groups. The magnitudes of the initial and terminal vectors of the group with a narrower QRS duration were greater, with the exception of the initial 40-msec. vector. The differences in direction are best demonstrated graphically in Figs. 2 and 3. It is apparent that these group differences are due to changes in angular speed. The ratio of the magnitude of each initial and terminal vector in the two groups to the mean QRS-

vector magnitude is shown in Table VI, the spatial angles produced by the mean QRS vector and each initial and terminal vector in Table VII, and the linear speed in Table VIII.

The results shown in Tables VI to VIII and in Figs. 2 and 3 show that for clinical application of initial and terminal vectors the total QRS duration must be considered.

TABLE V. SIGNIFICANCE TEST FOR THE DIFFERENCES OF INITIAL AND TERMINAL VECTORS BETWEEN NARROW AND WIDE QRS GROUPS (T-TEST)

		AZIMUTH	ELEVATION	MAGNITUDE
Initial Vector	0.01″	1.4398	0.6308	2.7644**
	0.02″	2.1071*	0.6756	3.4023**
	0.03″	3.0461**	0.4411	3.6776**
	0.04″	2.7224**	0.2692	0.7726
Terminal Vector	0.01″	1.1834	0.2094	5.7638**
	0.02″	1.5126	0.6746	6.0095**
	0.03″	3.1968**	2.5137*	4.5692**
	0.04″	5.5404**	4.1492**	3.9972**

*P: .05.
**P: .01.
The numbers in this table indicate numbers of t.

TABLE VI. RATIO OF MAGNITUDE OF THE MEAN QRS VECTOR AND EACH INITIAL AND TERMINAL VECTOR IN NARROW AND WIDE QRS GROUPS

		NARROW QRS GROUP	WIDE QRS GROUP
Initial Vector	0.01″/Mean	0.092	0.124
	0.02″/Mean	0.240	0.335
	0.03″/Mean	0.590	0.780
	0.04″/Mean	0.963	0.985
Terminal Vector	0.01″/Mean	0.077	0.169
	0.02″/Mean	0.209	0.391
	0.03″/Mean	0.411	0.648
	0.04″/Mean	0.571	0.842

TABLE VII. SPATIAL ANGLES BETWEEN MEAN QRS AXIS AND EACH INITIAL AND TERMINAL VECTOR IN NARROW AND WIDE QRS GROUPS

		NARROW QRS GROUP	WIDE QRS GROUP
Initial Vector	0.01″	121	141
	0.02″	68	96
	0.03″	36	48
	0.04″	13	26
Terminal Vector	0.01″	86	104
	0.02″	84	92
	0.03″	63	89
	0.04″	15	79

In this regard it is of interest that Pipberger[1] in his presentation noted that the initial 10 and 20-msec. QRS vectors showed such scatter that no analysis could be made. Although a wide scatter in the total group was noted, this scatter was reduced when the total group was divided according to total QRS duration. Electrical position exerted less effect in this scatter. In general, however, our data are in agreement with those found by Pipberger. The terminal QRS vectors were not evaluated by Pipberger.

Table IX shows the mean values and standard deviations of the azimuth,

TABLE VIII. DISTANCES OF VECTOR END POINTS OF EACH SUCCESSIVE INITIAL AND TERMINAL VECTOR IN NARROW AND WIDE QRS GROUPS

		NARROW QRS GROUP	WIDE QRS GROUP
Initial Vector	0″—0.01″	1.32	0.95
	0.01″—0.02″	3.00	1.96
	0.02″—0.03″	5.67	4.80
	0.03″—0.04″	5.18	5.20
Terminal Vector	0″—0.01″	1.81	0.79
	0.01″—0.02″	2.38	1.44
	0.02″—0.03″	3.60	2.13
	0.03″—0.04″	7.22	2.22

TABLE IX. MEAN VALUES AND STANDARD DEVIATIONS OF AZIMUTH, ELEVATION, AND MAGNITUDE OF EACH INITIAL AND TERMINAL VECTOR IN THE THREE DIFFERENT HEART POSITIONS

		VERTICAL POSITION			INTERMEDIATE POSITION			HORIZONTAL POSITION		
		H.	V.	MAG.	H.	V.	MAG.	H.	V.	MAG.
Initial Vector	Mean	+104.0	114.3	0.900	+120.5	95.1	1.220	+108.8	75.8	1.114
	S.D.	23.7	25.9	0.628	28.0	20.4	0.853	41.0	19.5	0.609
	Mean	+66.1	92.7	2.838	+76.1	81.8	2.975	+61.9	75.4	2.829
	S.D.	29.9	13.8	1.651	31.8	14.8	1.261	32.2	15.1	1.528
	Mean	+31.2	67.9	6.950	+27.8	72.9	7.007	+17.4	80.0	6.862
	S.D.	18.0	16.0	2.521	21.2	10.1	2.547	30.7	7.8	2.509
	Mean	−4.5	52.6	10.694	+1.3	65 8	10 245	−8.9	82.2	9.729
	S.D.	23.8	11.8	2.470	20.1	9.6	2.950	32.9	8.8	2.688
Terminal Vector	Mean	−111.3	89.9	1.313	−105.1	91.4	1.230	−107.9	105.7	1.586
	S.D.	31.8	44.0	0.603	34.2	38.8	0.799	24.8	34.1	0.880
	Mean	−106.9	87.3	3.681	−99.7	94.7	3.061	−102.6	106.2	3.467
	S.D.	19.6	21.8	2.049	29.8	26.8	1.356	14.0	20.4	1.322
	Mean	−95.6	83.9	6.250	−93.2	87.4	5.316	−92.2	104.5	5.714
	S.D.	35.2	18.9	2.374	32.8	20.6	2.462	21.2	16.6	2.099
	Mean	−79.1	65.9	8.388	−64.9	76.2	7.275	−67.3	93.8	7.038
	S.D.	40.3	21.5	3.035	43.1	18.3	3.406	32.6	16.0	2.141

H.: Azimuth. V.: Elevation. Mag.: Magnitude.

elevation, and magnitude of the groups with horizontal, intermediate, and vertical electrical positions. The values for each vector were compared statistically. There was no significant difference in azimuth and magnitude, but there was, of course, a significant difference in elevation. The constructed vectorcardiograms shown in Fig. 4 demonstrate this difference. There was no significant difference in the angular or linear speed of loop rotation between these groups.

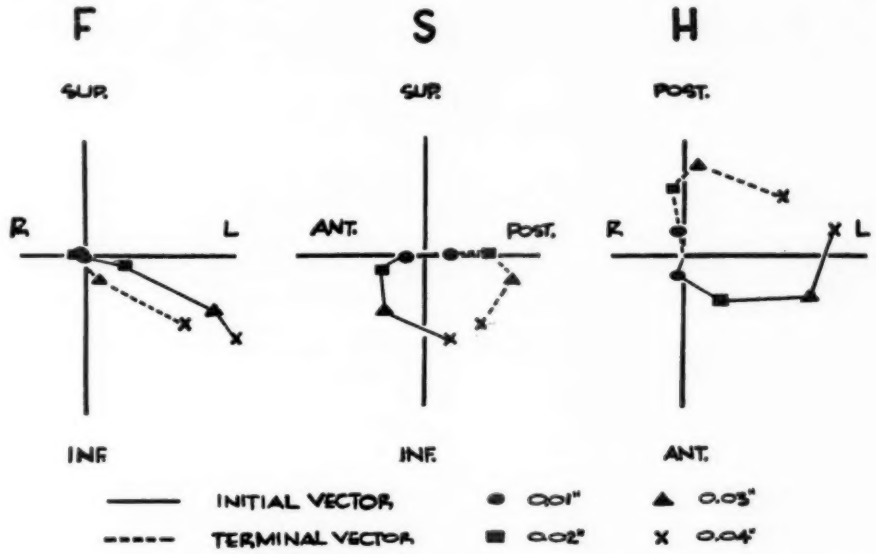

Fig. 2.—Vectorcardiograms constructed from the mean values of the amplitudes of the X, Y, and Z scalar leads of the SVEC-III system in the group with narrow QRS. *F* = frontal plane, *S* = sagittal plane, and *H* = horizontal plane.

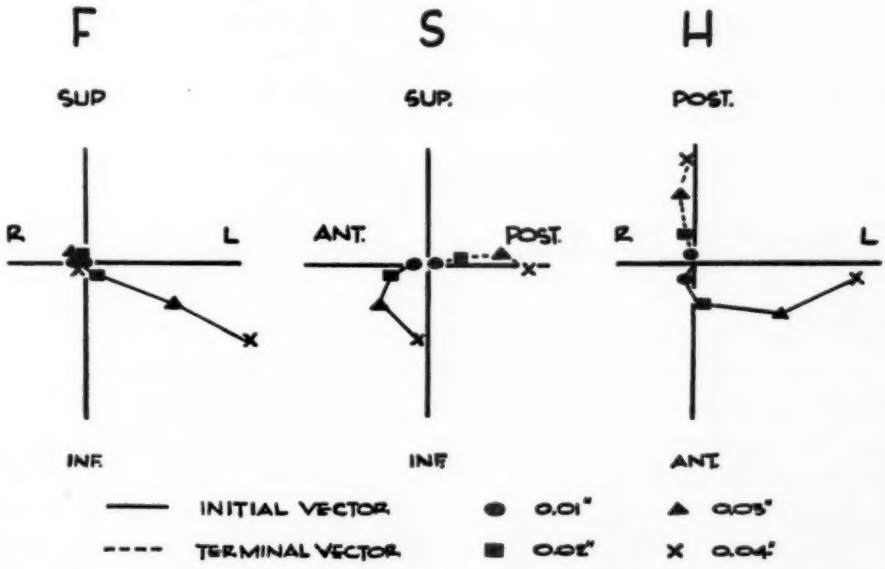

Fig. 3.—Vectorcardiograms constructed from the mean values of the amplitudes of the X, Y, and Z scalar leads of the SVEC-III system in the group with wide QRS. *F* = frontal plane, *S* = sagittal plane, and *H* = horizontal plane.

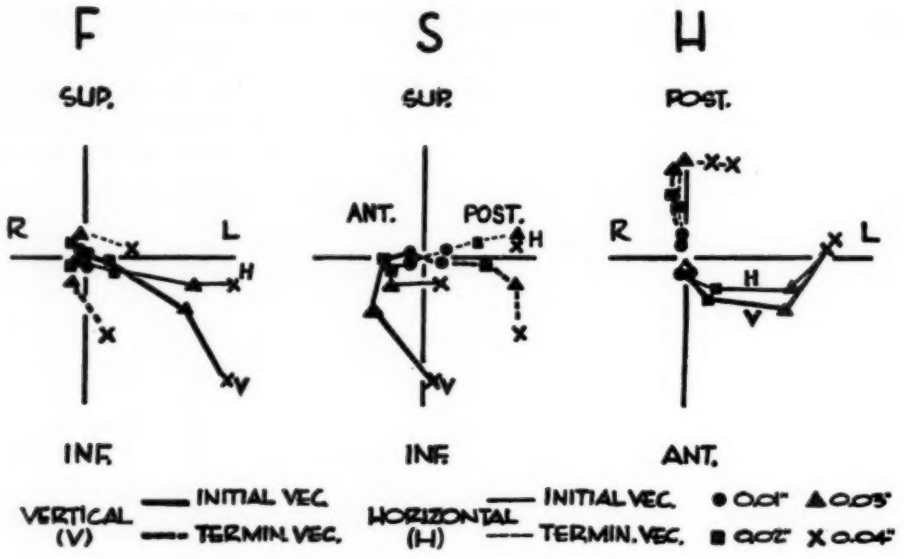

Fig. 4.—Vectorcardiograms constructed from the mean values of the amplitudes of the X, Y, and Z scalar leads of the SVEC-III system in the vertical and horizontal heart position. *F* = frontal plane, *S* = sagittal plane, and *H* = horizontal plane.

DISCUSSION

The main purpose of these data is to provide quantitative information regarding initial and terminal vectors in a sufficiently large normal group to serve as a basis for clinical application. We selected a group of healthy older men, because in the older age range the incidence of heart disease is highest. In previous work, a significant effect of age was found in the conventional scalar (time-based) electrocardiogram[4] and mean spatial vectors.[5] It is reasonable to assume that initial and terminal vectors will also be affected by age, but consideration of this assumption was outside the scope of the present study. The data as presented in this study, therefore, are valid only for the comparison of elderly healthy people with patients. For clinical evaluation, only the difference between patients and healthy people of the same age is relevant, otherwise the differentiation between physiologic age trends and pathologic conditions would be difficult. This has been discussed in greater detail in a previous communication.[6]

The results show that in normal older men the 40-msec. initial vector is virtually identical with the mean QRS vector, so that the instantaneous 20-msec. and 30-msec. vectors are more representative of the initial processes.

The significant differences between initial and terminal vectors in both magnitude and direction for the groups with wide and narrow QRS duration are important for clinical application. The QRS duration in normal adult people shows a rather large range, from 0.06 to 0.11 second, or even larger if the spatially corrected QRS duration[7] is used. Correction as to the QRS duration considerably reduces the normal scatter and makes, therefore, the evaluation of abnormal variations more accurate. This is true also for the correction as to the "electrical position."

The data of initial and terminal angular and linear speeds are expected to be useful in the recognition of comparatively minor ventricular conduction defects.

SUMMARY

1. The initial and the terminal 10, 20, 30, and 40-msec. vectors of the QRS complex were statistically analyzed in 93 normal older men. These initial and terminal vectors were presented as mean values of azimuth, elevation, and magnitude, with standard deviations for each angular and linear speed of the sweep.

2. The initial QRS vectors point more forward, the terminal QRS vectors point more backward, and the magnitude of all instantaneous initial and terminal vectors is smaller in a group with wide QRS than in a group with narrow QRS.

3. The electrical axis in the frontal plane did not correlate with azimuth, magnitude, or angular or linear speed of the initial or terminal vectors.

4. The initial 40-msec. vector and the mean QRS vector are so similar in direction and magnitude that the 40-msec. vector cannot be truly considered as an initial vector.

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Circulatory Disturbances in Life-Threatening Poliomyelitis

William A. Spencer, M.D., Robert R. Jackson, M.D., Carlos Vallbona, M.D., and Gunyon M. Harrison, M.D., Houston, Tex.

Disturbances of the action of the heart and the systemic and pulmonary circulations contribute to mortal processes in the poliomyelitis patient with viral invasion of the brain stem or with severe respiratory insufficiency. The complex nature of the circulatory disturbances in these patients suggests that it would be useful to consider, first, practical experience with the diagnosis and therapy of major circulatory abnormalities, and, secondly, a review of the patterns of their occurrence and the circumstances in which they have been observed.

This paper describes the experiences with cardiovascular disturbances obtained in a regional respirator center that has admitted over 1,490 patients with acute poliomyelitis. This presentation reflects the contributions of many students of poliomyelitis. As such a descriptive effort it represents one method of management utilized in a respirator center. It includes current techniques and definitive procedures based on useful hypotheses that have been suggested by clinical investigation and animal experimentation.[1] The reader is referred to the review article on this subject by Weinstein,[2] in which numerous bibliographic references are given.

INCIDENCE AND GENERAL CONSIDERATIONS

Bedside experience indicates that respiratory muscle paralysis, impairment of swallowing, and disturbances of respiratory regulation are allied with circulatory disturbances and pose a threat to life. Of a total of 357 individuals with life-threatening poliomyelitis, approximately one third (126) had circulatory disturbances of one or several types. Because 52 of the 59 fatalities (16.5 per cent) in the entire life-threatened group had such disturbances, it is inferred that mortality goes hand-in-hand with these circulatory complications. The actual numerical incidence of various circulatory disturbances, ordered according to relative frequency of occurrence, is shown in Table I. These incidence figures

From the Southwestern Poliomyelitis Respirator and Rehabilitation Center, the Texas Institute for Rehabilitation and Research, and the Departments of Rehabilitation, Physiology, and Pediatrics, Baylor University College of Medicine, Houston, Tex.

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are not mutually exclusive, since combinations of these conditions are apt to occur in the same individual. This table indicates also the percentage of fatality with a particular complication regardless of its frequency. It does not imply that the complication itself is the cause of death, which may be the result of manifold causes.

TABLE I. TYPE AND RELATIVE FREQUENCY OF CIRCULATORY DISTURBANCES OBSERVED IN 357 PATIENTS WITH LIFE-THREATENING POLIOMYELITIS

TYPE OF DISTURBANCE	INCIDENCE	ASSOCIATED PER CENT OF MORTALITY
Cardioregulatory disturbances and vasomotor lability	78	35
Hypertension of any degree	69	27
Myocardial insufficiency	58	36
Hypotension	50	72
Cutaneous vasoconstriction and hyperthermia greater than 105° F. (rectal)	34	68
Gastrointestinal bleeding—hematemesis or melena	27	48
Pulmonary edema	11	89
Total incidence of circulatory disturbances	327	
Total number of individuals with one or more circulatory disturbances	126	
Total fatalities	52	

PATHOGENESIS

Cardioregulatory and vasomotor disturbances often develop concurrently with lower brain-stem involvement of the swallowing regulatory centers and motor nuclei. This has been frequently observed clinically and confirmed by neuropathologic examinations. There may be destruction of vasomotor and cardioregulatory areas of the brain-stem reticulum with the invasion of the medulla and pons by the virus. On the other hand, circulatory disturbances are also commonly associated with respiratory insufficiency in its terminal stages. Biochemical alterations, particularly hypoxemia, can produce functional disturbances of the central nervous system. Also, extreme or rapid shifts of extracellular pH and carbon-dioxide concentrations may impair activity of the neurons as well as that of other tissues. When regulatory or compensatory responses induced by serious malfunction of the cardiovascular system itself are also superimposed, a complex pattern of causation emerges. For these reasons, clinical investigation and experience may tend to substantiate one or another cause of cardiovascular disruption as prepotent in any individual patient. It is also likely that the processes of disease, the physiologic effects of treatment procedures, and the aggregation of complications have a variable timetable. In consequence of this, and for practical purposes, prompt syndromic treatment is a paramount clinical rule. The early use of artificial respiration and, therefore, the prevention of ultimate respiratory failure and asphyxia is a most important anticipatory measure. Unmodifiable virus destruction of vital regulatory neurons can be accepted only upon exclusion or correction of all possible contributory conditions.

DIAGNOSIS

The diagnosis of cardiovascular abnormalities in the course of severe poliomyelitis depends upon careful and accurate recording of pulse rate, blood pressure, and temperature, even in the tank-respirator patient. It has been of special value to make these observations at frequent intervals in the extremely ill patient.[3] Considerable attention should be given to the color and temperature of the skin. Flushing of the ear after pressure-blanching gives an indication of vascular stability.

The staff of the respirator center has placed considerable emphasis upon the value of serial electrocardiograms, obtainable even in the apneic patient in the tank-respirator. The direct-writing instruments, especially those with two channels permitting simultaneous recording of the electrocardiogram with the apical heart sounds or the carotid pulse, are particularly valuable in assessing myo-

TABLE II. INCIDENCE OF CHANGES IN SERIAL ELECTROCARDIOGRAPHIC AND PHONOCARDIOGRAPHIC MEASUREMENTS IN PATIENTS WITH ACUTE LIFE-THREATENING POLIOMYELITIS

MEASUREMENT AND CONDITION	INCIDENCE (PER CENT)
Rhythm:	
Sinus tachycardia	27
Sinus bradycardia	17
Wandering pacemaker	7
Premature beats of ventricular origin	6
Supraventricular tachycardia	1
Scalar:	
P-R interval prolongation	6
QRS interval prolongation due to bundle branch block	9
Q-T interval prolongation	28
Q-T interval shortening	7
Vector: (direction and magnitude)	
Shift to the right of the P vector	15
Shift to the left of the P vector	6
Shift to the right of the QRS vector	22
Shift to the left of the QRS vector	3
Decreased magnitude of the T vector	5
Separation greater than 60° between QRS and T vectors (frontal)	53
Systolic duration: (relative to heart rate)	
Systolic prolongation	11
Systolic shortening	41

These figures are based on the analysis of serial electrocardiograms and phonocardiograms in the last 100 patients with acute life-threatening poliomyelitis. The diagnostic criteria for some of the conditions indicated in this table were the following: Sinus tachycardia was considered present when the heart rate exceeded 130 per minute in adults or 160 per minute in children. Severe tachycardia (greater than 200 in children and 180 in adults) was observed in 4 per cent of the cases. Relative sinus bradycardia was diagnosed in the presence of a heart rate of less than 80 per minute concomitant with a body temperature in excess of 103° F. A prolongation of the P-R interval was diagnosed when the values exceeded those indicated by Lepeschkin.[13] Q-T prolongation or shortening was diagnosed if the values were higher or lower than those predicted according to the formula proposed by Hegglin and Holzmann.[14] A shift to the right or to the left of the frontal projection of the vectors of P, QRS, and T was diagnosed when a deviation to the right or to the left in excess of 15 degrees was observed in successive electrocardiographic recordings. Systolic prolongation and systolic shortening were diagnosed when the duration of the mechanical systole departed from normal values predicted according to the formula proposed by Hegglin.[8]

cardial activity (see Table II). The electronic amplifying stethoscope permits evaluation of heart sounds in the patient confined to the tank-respirator and auscultatory measurement of the blood pressure. A special cuff for such determinations has been developed. It contains an internal acoustic transducer for detection and amplification of the Korotkoff sounds.[4]

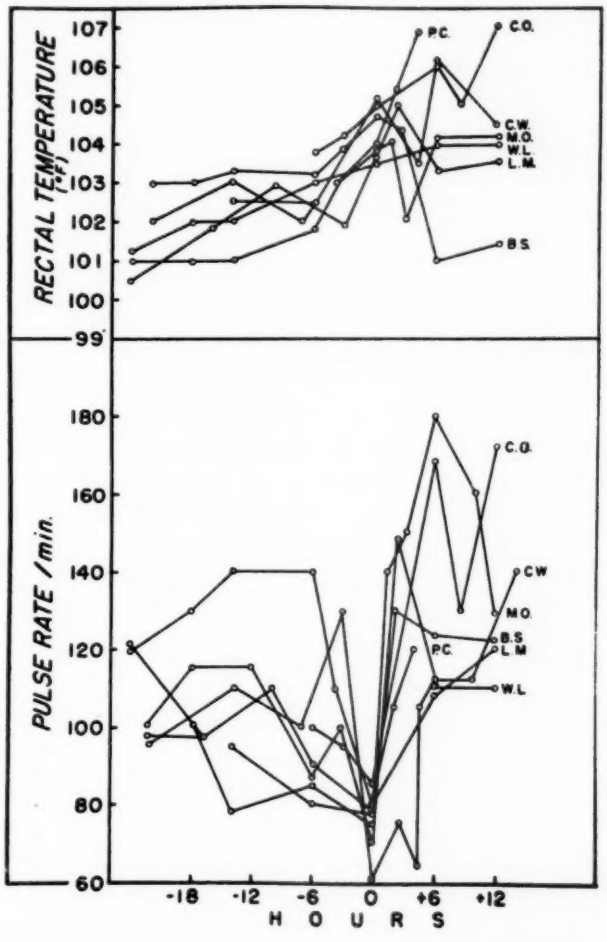

Fig. 1.—Pulse rate and body temperature relationship of poliomyelitis patients with bradycardia. The pulse rate of 7 poliomyelitis patients with swallowing difficulty and bradycardia is related to the rectal body temperature. The individual pulse rate and temperature records were arranged so that the occurrence of minimum pulse rate (bradycardia) was designated zero time, and the measurements in hours before and after the occurrence of bradycardia could be seen in proper relation.

Fluoroscopic facilities should be available in the acute unit. Fluoroscopy can be done on the patient receiving cuirass-respirator respiration or intermittent positive pressure breathing (IPPB). Evaluation of heart size and the presence of pulmonary congestion can be detected by chest radiographs made with the patient on the carriage of the respirator, although estimations carried out by these means are not accurate.

Measurements of circulation time may yield valuable information in some cases. Ear oximetry is of paramount value in detecting slight degrees of hypox-

emia, and differentiates arterial hypoxemia from peripheral vasoconstriction and circulatory stasis leading to cutaneous cyanosis in patients with adequate arterial oxygenation.

Determination of arterial blood pH, oxygen and carbon-dioxide content and tension, together with an analysis of expired gas, have usefulness in patients with disturbances of both pulmonary ventilation and circulation. In this connection, microtechniques performed on small arterialized ear blood samples have been successfully utilized.[5] Serial determinations of serum electrolytes may be needed to detect electrolyte changes important in myocardial function. Contributory pulmonary complications may be detected by serial determinations of respirator pressure/lung volume changes.[6]

Regulatory Disturbances of Cardiac and Vasomotor Activity.—The most common alteration of cardiovascular activity is *sinus tachycardia* out of proportion to body temperature. Rapid, thready pulse is a finding in patients with severe respiratory insufficiency and in the respirator patient with vasomotor incompetence. Marked lability of heart rate is found often in the acute phase of life-threatening poliomyelitis. *Bradycardia* is seen less frequently, and usually as a transitory condition succeeded by tachycardia. It occurs usually in individuals with swallowing impairment and may be concomitant with hyperthermia and severe cutaneous vasoconstriction (see Fig. 1). The rhythmicity of the heart may be greatly affected. An exaggerated respiratory arrhythmia is observed occasionally in the patient confined to the tank-respirator. In other instances, the electrocardiographic analysis of the heart rhythm reveals the existence of sinus arrhythmia, a wandering pacemaker, or extrasystoles of different origins.

Disturbances of the vasomotor system are more difficult to evaluate, since only the blood pressure, pulse, and cutaneous circulation are accessible indicators. From a clinical viewpoint, severe *cutaneous vasoconstriction* is often associated with hyperthermia. Less important but alarming disturbances such as the suffusion of the facies and flushing should be recognized, since they are often related to hyperventilation and respiratory alkalosis or to excessive constriction of the neck by tank-respirator collars. Occasionally, a patient may have alternate periods of cutaneous pallor and erythema. This may accompany an equal lability of blood pressure and is of serious prognosis.

In the patient in the acute phase it is likely that *hypertension* is a consequence of disturbances of vasomotor regulation in the central nervous system. The most severe forms of hypertension commonly occur in the patient with swallowing impairment; hence, there is substantial evidence for brain-stem viral involvement. Less severe degrees of hypertension have been observed to accompany early respiratory insufficiency and may be compensatory in nature. Occasionally, a clear sequence of events will develop, consisting of progressive elevation of blood pressure followed by declining blood pressure. This situation has been observed to coincide with the development of acute heart failure and pulmonary edema (see Fig. 4). It is extremely rare for hypertension to persist long enough to produce encephalopathy, since it is usually corrected rapidly by appropriate pharmacologic measures.

Hypotension is a very grave occurrence. It may accompany rapidly progressing lethal disease or the use of artificial pressure breathing of any type. Hypotension may result from insufficient vasomotor compensation. This compensation is necessary to promote systemic venous return to the heart and overcome the deleterious effect of artificial respiration. Often, suitable correction of this condition can be obtained with pharmacologic agents.

Disturbances of the pulmonary circulation, such as *pulmonary congestion*, are identified by indirect means. The serial electrocardiogram and the chest x-ray film are especially helpful. Ventilatory measurements of the type used to estimate the relative distensibility of the lungs[6] are also useful. The electrocardiogram may indicate changes in the magnitude of the P vector and shifts to the right of the frontal projections of the mean P and QRS vectors.

Myocardial Disturbances.—Diagnosis of disturbances of cardiac activity in the course of acute poliomyelitis rests firmly upon clinical estimates of cardiac function and electrical activity. Dependence upon cardiac enlargement as an index of myocardial insufficiency is less reliable in poliomyelitis than in some other conditions. Percussion is difficult to carry out. Portable x-ray films are far from satisfactory for accurately estimating cardiac configuration and size.

The ECG may suggest myocardial disturbances if the magnitudes of the vectors of QRS and T are small, if there is progressive separation of the QRS and T vectors, or prolongation of the Q-T time. It is possible to obtain some information on the mechanical activity of the myocardium by simultaneous registration of the electrocardiogram and the phonocardiogram.[7] An estimation of the duration of mechanical systole can be made by computation of the interval between the onset of the QRS complex and the onset of the second heart sound. Such measurements in patients with acute poliomyelitis have revealed remarkable changes in the duration of the mechanical systole, both absolutely and relatively, according to the heart rate. In general, output insufficiency is suspected at very rapid heart rates with extremely short systolic duration.[8] In this situation, high levels of blood 17-OH corticosteroids have been found in some of these acutely ill patients.[9] The influence of this upon the duration of the cardiac contraction requires further investigation as a pathogenic factor in acute, overwhelming disease states. Relative changes of duration of mechanical systole do not necessarily parallel the duration of the Q-T time, so that a short systole may coincide with a prolonged Q-T, or vice versa; hence, Q-T times have not been reliable.

In the present state of knowledge it is difficult to correlate these different changes with pathologically demonstrable lesions of the myocardium or conduction systems. The fact that these changes have an extreme chronological variation in the same individual suggests the possibility that they are related to concurrent dynamic changes such as ischemia or cellular metabolic disturbances and altered neural regulation, rather than to components of any typical pathologic process.

Autonomic Disturbances.—Parallel autonomic dysfunctions may accompany circulatory disturbances and are, therefore, part of syndrome complexes. Gastrointestinal bleeding is the most readily recognized of the clinical examples and is considered to be due to vagal hyperactivity. This condition is of variable degree

but can lead to massive loss of blood and shock. Paralytic ileus and gastric atony are even more common and often associated with gastrointestinal bleeding.

TREATMENT

It has been noted in recent years that satisfactory treatment of the most serious disturbances can be successfully carried out. Survival in the presence of usually lethal complications may be attributed to many factors. The relationship of favorable results to any specific treatment must be viewed with great caution. The declining incidence of circulatory catastrophe may be cited. Generally, it has paralleled earlier use of artificial respiration, better control of airway obstruction, improvements in respiratory equipment and its usage, employment of spirometric measurements to estimate ventilation, study of gas exchange, and the avoidance of overtreatment. Furthermore, general supportive measures, proper regulation of fluid and electrolyte homeostasis, control of secondary infections, and many other valuable elements have been recognized as important in preventing or minimizing circulatory disturbances.

The following outline summarizes the plan of treatment that we have used for each circulatory complication.

Cardioregulatory and Vasomotor Instability.—Usually, no treatment is indicated for sinus tachycardia. If the heart rate becomes extremely rapid, the underlying cause should be sought out and corrected.

Sinus bradycardia is generally transitory in nature and requires no treatment. Bradycardia may appear as evidence of hypoxemia in poliomyelitis patients (see example in Fig. 7). Modifiable conditions leading to hypoxemia should therefore be corrected by ventilatory adjustments or the use of increased concentration of oxygen in the inspired air. If bradycardia persists, it may be treated with vagal blocking agents other than atropine, which is contraindicated because of its drying effect upon the mucous membrances and its production of thick, ropy secretions. Agents such as the methantheline derivatives (Banthine) are preferred, especially if there is an associated massive gastrointestinal bleeding. A dose is administered immediately, intravenously and slowly, in the range of a total of 5 to 10 milligrams. The parenterally administered drug should not exceed a concentration of 5 milligrams per milliliter of diluent. Peripheral and apical pulse should be observed so as to control the speed of injection. This dose may be repeated in 30 minutes if the bradycardia does not revert.

Cooling of the body should be attempted in order to control elevation of the body temperature to levels exceeding 104° F. (rectal). This anticipatory measure may prevent episodes of bradycardia. Procedures and agents that promote cutaneous vasodilation and loss of heat from the surface of the body may be effective. Acetylsalicylic acid has not been valuable and may produce a sudden decline in temperature to hypothermic levels. Brushing the skin with a surgical scrub brush improves the skin circulation through the activation of the local axon reflex. Solutions of 5 per cent alcohol in 5 per cent dextrose intravenously seem to be a valuable adjunct. Rarely more than 500 to 1,500 ml. of such solutions are needed.

If gastrointestinal bleeding is detected in vomitus, or if ileus is present, a nasogastric tube should be placed in the stomach and constant gastric decompression maintained.

Hypotension.—Hypotension is usually effectively treated with the continuous intravenous administration of a solution containing norepinephrine (Levophed), administered in doses of 4 to 8 milligrams diluted in 1,000-ml. quantities of 5 to 10 per cent dextrose in water or saline. In general, other varieties of vasopressors have been less effective than norepinephrine. The rate of administration of norepinephrine is directly determined by the blood pressure response (systolic pressure alone can be suitably utilized as a guide in the tank-respirator patient). If an intravenous infusion cannot be started immediately, or cannot be safely maintained, the subcutaneous administration of 2 per cent phenylephrine hydrochloride (Neo-Synephrine) at doses of 1 to 2 c.c. every 2 to 4 hours is recommended. In some instances the use of vasopressors will be necessary for several days or even weeks. The drug is gradually decreased in amount, and progressively longer intervals are tried without treatment.

The hypotension that occurs during artificial respiration may be ameliorated by careful evaluation of ventilatory requirements and adjustment of the respirator. Careful recording of blood pressure and measurements of tidal ventilation in these circumstances will establish the safest equipment settings. It is also important to keep the mean pressure in IPPB equipment as close to atmospheric as possible by altering positive and negative phases in suitably adapted equipment. Similarly, the tank-respirator may be adjusted so that there is a positive pressure on expiration equal to that employed in the inspiratory phase (e.g., respirator setting of -12 cm. of water on inspiration, and $+12$ cm. of water on expiration).

Hypertension.—Elevations of systolic pressure above 180 mm. Hg in adults or 150 mm. Hg in children, or above 100 mm. Hg diastolic in adults or 90 mm. Hg in children, warrant treatment. The parenteral administration of derivatives of Rauwolfia serpentina has been successfully used in this situation. Rescinnamine for parenteral use is employed intravenously in a dosage range of 100 to 160 micrograms per kilogram of body weight per 24 hours. One fourth of the calculated dose is administered immediately, and an effect usually follows within 30 minutes to 2 hours. This dosage may be repeated in 2 hours if needed. The balance of the 24-hour dose is given within 6 to 8 hours, and continuation of the drug is rarely necessary for more than 24 hours. Drug therapy with ganglionic blocking agents of the hydralazine or hexamethonium variety is contraindicated.

Myocardial Insufficiency.—As has been indicated in the discussion of the causes of myocardial insufficiency, the treatment of this condition cannot be separated from the treatment of contributory events. Once such contributory circumstances have been corrected or ruled out, the pharmacologic support of heart action may be clinically indicated. The two most useful drugs appear to be digitalis and derivatives of Rauwolfia serpentina. These drugs are rarely employed together. Digitalis may be indicated in the presence of a rapid, unmodifiable heart rate in which phonocardiography established the existence of prolonga-

tion of mechanical systole. Conventional dosage should be employed with the caution that some poliomyelitis patients with myocardial involvement appear to be sensitive to digitalis action. A decrease in heart rate, together with improvement in the quality of the heart sounds and shortening of the duration of systole may be considered beneficial signs. The maintenance dose is rarely necessary on a daily basis for more than 7 to 14 days.

It is also extremely important to avoid the rapid administration of large volumes of intravenous fluids. Continuous administration of fluids at minimal rates is advisable.

The usefulness of Rauwolfia serpentina extracts in the instance of severe tachycardia depends upon its central action on cardiac rate, the improvement of coronary blood flow, and its effect upon duration of the systole.[10-12] Dosage is similar to that given for the treatment of hypertension. It is usually needed for only 24 to 48 hours. It appears to be most beneficial when extreme tachycardia is associated with relative *shortening* of the mechanical systole.

Acute Pulmonary Edema.—Acute pulmonary edema has been uncommon in our clinical experience, although postmortem evidence would suggest that it occurs fairly frequently in fatal disease. Avoiding the use of plasma, plasma expanders and whole blood may be factors in minimizing acute circulatory overloading and the production of pulmonary edema. A terminal circulatory collapse usually follows the appearance of pulmonary edema. If artificial respiration has not been employed, it is indicated immediately, since edema leads to prompt impairment of pulmonary gaseous diffusion. Intermittent positive pressure breathing may ameliorate the symptoms and beneficially reduce the effect of fluids in the tracheobronchial tree and alveoli. We have combined intermittent positive pressure breathing and the tank-respirator with the addition of high concentrations of oxygen in a few instances, with limited success. The slow intravenous administration of aminophylline in a dosage range of 0.1 to 0.5 Gm. in 5 to 50 c.c. of 50 per cent glucose solution may be helpful if it is combined with effective ventilation and measures to sustain blood pressure. Rotation of tourniquets on the extremities may be employed. The use of aerosols of 95 per cent alcohol or antifoaming agents may contribute to keeping a patent airway.

CLINICAL EXAMPLES OF THE PATTERN OF CARDIOVASCULAR DISTURBANCES IN POLIOMYELITIS

The particular sequence of events describing the pattern of cardiovascular alterations that may occur in an individual patient is illustrated in the following examples. They have been chosen from both fatal and nonfatal cases in order to indicate the most common varieties of cardiovascular dissolution. The relative significance of these disturbances is contrasted to the degree that case examples permit. Records have been chosen to demonstrate apparently successful treatment or the occurrence of spontaneous reversion which may be associated with death in one or survival in another.

Fig. 2 summarizes the circulatory findings in a 14-year-old patient with bulbar poliomyelitis who was admitted to the hospital 48 hours after the onset of severe, untreated swallowing impair-

ment and respiratory insufficiency. The patient was moribund on admission, in coma, and had arterial and cutaneous cyanosis and apnea. Records of spontaneous ventilation revealed an irregular rate and pattern of breathing, with long periods of apnea and a minute volume of only 3 to 4 liters. In spite of the obvious initial underventilation there was an arterial pH of 7.53, a CO_2 content of 11.4 mM./L., and a pCO_2 of 12 mm. Hg.* An emergency tracheotomy was performed, and artificial respiration by tank-respirator instituted immediately. Aspirated oral secretions in the trachea and bronchi were removed by endobronchial suction. His minute volume increased to 8 to 10 liters. Blood pressure was unobtainable and norepinephrine was administered intravenously in a concentration of 4 mg./500 c.c. of 5 per cent dextrose at rapid drip. Thereafter, blood pressure could be obtained on only two occasions. Terminal processes included bradycardia, hypotension, tachycardia, hyperthermia, and ECG evidence of marked left ventricular preponderance. All efforts to decrease the hyperthermia failed and cardiac activity ceased. This example is cited to point out the difficulty of separation of the terminal respiratory and circulatory events into causes other than the asphyctic state itself.

Fig. 3. illustrates the entire constellation of cardiovascular disturbances. These occurred in a 28-year-old individual with severe swallowing difficulty, and virtually total muscular paralysis. Immediately after admission, artificial respiration was required, followed by tracheotomy. Viral invasion of the brain stem was suspected at the time of admission in 1951, but the premonitory character of the subsequent circulatory changes was appreciated only in retrospect. There was a brief episode of bradycardia and hyperthermia 12 hours after admission that clearly heralded medullary involvement in the presence of swallowing difficulty. The administration of Banthine at point *A* may or may not have influenced the reversion of the pulse rate to a rate more appropriate for the body temperature. Serial electrocardiograms obtained before, during, and after the bradycardic episode indicated a shifting of the QRS vector, with patterns of intermittent right bundle block changing from *beat to beat*. By the second hospital day the patient's condition appeared to stabilize. The pulse rate was uniform, and systolic hypertension gradually subsided. Early in the third day (at point *C*) the patient received an intravenous preparation of amino acids (Aminosol), which was followed by a sudden drop in the systolic blood pressure. Late in the third day the pulse and blood pressure were stable and the ECG revealed a normal sinus rhythm. The frontal projection of the QRS vector was at +25 degrees. The patient developed an episode of cyanosis, and bronchospasm was suspected from ventilatory studies. This condition was treated with the subcutaneous administration of ephedrine sulfate (point *B*). Twelve hours later, without any clinical signs of respiratory insufficiency, a sudden episode of hypertension with an increase in pulse rate developed, and the patient expired immediately.

Postmortem neurohistologic examination of the brain stem revealed a profusion of foci of inflammation and extensive neuronal depopulation and damage. The most affected areas included the dorsal motor nuclei of the vagus, the hypoglossal nuclei, the nuclei of the tractus solitarius, the nucleus ambiguus, and the medial portion of the reticular formation. It is particularly pertinent that this example included nearly all of the cardiovascular disturbances described before, and was observed to develop in the presence of well-defined anatomic lesions of the brain stem. The localization of lesions included those portions of the brain stem considered to constitute a large portion of the hierarchy of cardiovascular regulation, to wit: the medial reticular formation, field H_2 of Forel, central gray and lateral reticular formation of the midbrain, and the lateral vestibular nuclei of the medulla oblongata.†

Fig. 4 illustrates the sequential cardiovascular disruption in fatal acute poliomyelitis without respiratory involvement. Essentially normal values of cardiovascular activity were observed at the time of admission of this 18-year-old patient who had slight swallowing difficulty but no evidence of respiratory muscular paralysis or involvement of other muscle groups. Eleven hours after admission, bradycardia developed, and thereafter, the body temperature and systolic and diastolic blood pressures increased. At the peak of the hypertensive episode, indicated in the

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***Normal range for these values in our laboratory are: pH, 7.35 to 7.45; CO_2 content, 23 to 25 mM.; and pCO_2, 35 to 45 mm. Hg.**

†The authors acknowledge the assistance of Dr. John H. Perry, Associate Professor of Anatomy, Baylor University College of Medicine, for the neuroanatomic description of the brain stem and medullary pathology in this example.

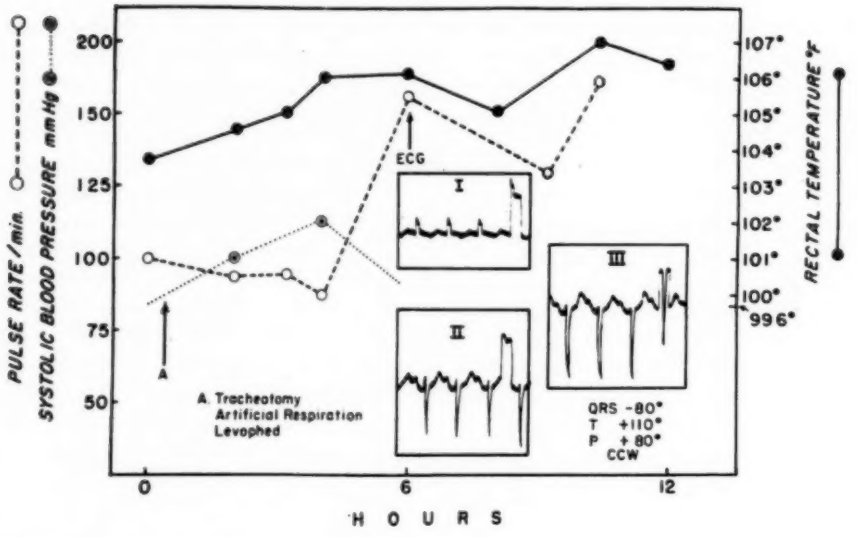

Fig. 2.—Pulse rate, blood pressure, and body temperature in terminal stages of respiratory insufficiency due to swallowing impairment, with tracheobronchial aspiration. The pulse rate, blood pressure, and body temperature are related to time from admission to the hospital. A representative ECG record (Leads I, II, and III) is shown.

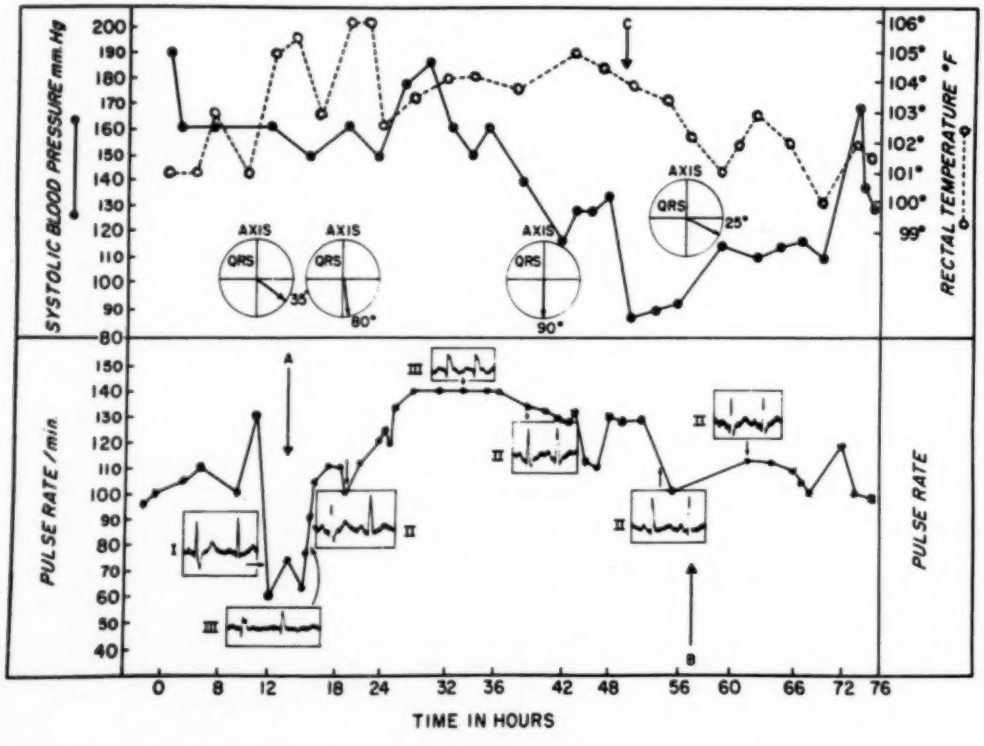

Fig. 3.—Bradycardia, hypertension, hypotension, cardiac conduction defects, and hyperthermia in bulbospinal poliomyelitis with neuropathologic evidence of medullary involvement. Serial pulse rate, blood pressure, body temperature, and representative serial electrocardiograms are oriented in relation to time from admission. At point *A*, Banthine was administered; at point *B*, ephedrine sulfate, and at point *C*, intravenous amino acid solution.

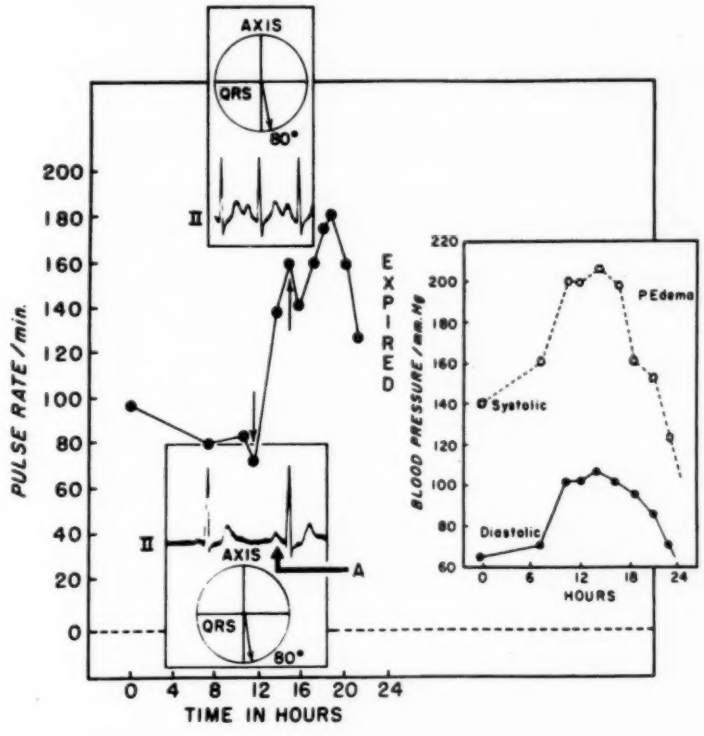

Fig. 4.—Bradycardia, hypertension, and pulmonary edema in rapidly progressing poliomyelitis. Pulse rate changes, and blood pressure elevation and decline are indicated in relation to time from onset. Representative ECG records were obtained at the points indicated by arrows. At point *A* a shifting auricular pacemaker is identified.

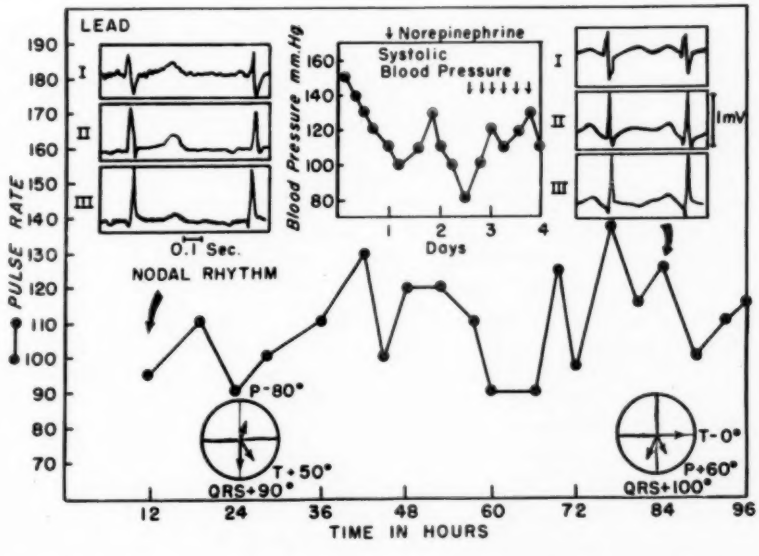

Fig. 5.—Marked vasomotor and cardiac lability in a poliomyelitis patient surviving swallowing difficulty, respiratory irregularity, respiratory muscle paralysis, and coma with convulsions. Serial pulse rate values, blood pressure, and representative electrocardiograms are oriented according to time in hours from admission.

figure by *P. Edema*, the patient complained of "rattling in his chest." Respiration became labored and panting in character. Moist râles were auscultated throughout the lung fields, and he coughed up frothy, pink secretions. Blood pressure soon began to decline precipitously. He received one third of his calculated digitalizing dose of digitoxin. Electrocardiograms, indicated in the figure by arrows, showed, first, a shifting auricular pacemaker with nearly normal QRS axis; then, with increasing heart rate the standard limb and precordial leads indicated right ventricular preponderance, and a P vector of increased magnitude with shifting to the right. The pulmonary edema was associated with marked deterioration in the quality of the heart sounds. Blood pressure became unobtainable, and the patient expired 21 hours after admission. The application of the electrophrenic respirator was unsuccessful, and terminal arterial chemistries revealed slight carbon-dioxide retention although the pH remained within normal limits. The patient's arterial blood values were: pH, 7.36; CO_2 content, 30.1 mM.; and pCO_2, 55 mm. Hg. This individual was considered to have had rapidly progressing bulbar poliomyelitis with involvement of the central cardiac and vasomotor regulatory mechanism.

Fig. 5 shows the circulatory changes in a 19-year-old school girl who survived an extremely severe acute phase. The cardiovascular complications that ensued are comparable to those illustrated in the preceding fatal cases but were reversible. This individual had the onset of swallowing difficulty several hours prior to admission to the center. On arrival she had spotty muscular weakness and some impairment of respiratory musculature function, indicated by fluoroscopy and reduced vital capacity. She was very drowsy and her movements were uncoordinated. A tracheotomy was performed immediately after the initial evaluation, and following this she was placed in the tank-respirator. Two hours later she became comatose and remained in this condition during the ensuing 5 days. The restoration of her sensorium coincided with lysis of the elevated body temperature. During the course of respiratory management, serial oximeter determinations of arterial oxygen saturation indicated maintenance of normal values, except in two brief periods when she had grand mal type of seizures. These episodes responded promptly to the intravenous administration of sodium pentobarbital. On the first day the ECG revealed a nodal rhythm and normal QRS and T vectors. A precipitous drop in the blood pressure occurred on the third day, and as soon as the systolic pressure reached the level of 80 mm. Hg, a continuous intravenous infusion of norepinephrine was instituted. Blood pressure returned to normal levels, and the drug was required for 48 hours. By the fourth day the electrocardiogram indicated increasing right ventricular preponderance (QRS vector, +100 degrees; T vector, 0 degrees) (see second set of electrocardiograms in figure and axis circle below). Digitalis was administered, and a stabilization of the pulse and return of the ECG to normal patterns followed. After the acute phase had subsided, respiratory weaning programs and muscular rehabilitation proceeded in a progressive and satisfactory manner. Swallowing function was eventually regained, and the vital capacity increased to 80 per cent of expected values. The only residual muscular weakness involved the left lower extremity.

Fig. 6 depicts the cardiovascular changes in a case of spinal poliomyelitis with respiratory muscle paralysis. This patient had no detectable evidence of disturbed brain-stem function. There are some counterparts to the preceding example that should be noted. This 32-year-old housewife was admitted 3 days after the onset of poliomyelitis. On the day of admission, muscular paralysis with asymmetrical involvement of the trunk and all four extremities took place. Respiratory muscle paralysis was indicated by a vital capacity of 0.6 liter in the initial evaluation, and artificial respiration was started after a brief examination. The concomitance of relative bradycardia with hyperthermia (temperature of 105 degrees F., rectal) is indicated in the figure. There were no detectable changes in the electrocardiographic records (see first and second ECG Lead II samples in the figure). Body temperature declined following the episode of bradycardia, and there was a significant drop in the systolic blood pressure to 85 mm. Hg. Administration of vasopressor substances was not considered necessary since the blood pressure rose spontaneously to normal levels very soon thereafter. The ECG obtained in the ninteenth hour following admission indicated separation of the QRS and T vectors from previously normal values. The balance of the acute phase was uneventful. The patient was afebrile by the eighth day of hospitalization. The lowest vital capacity was 0.3 liter. A respiratory weaning program was carried out very slowly, and muscle re-education was carefully paced because of residual myocardial damage. This was in-

dicated by subsequent serial electrocardiographic and phonocardiographic abnormalities and by average fast pulse rates in spite of complete inactivity. Six months after onset of the disease she had progressed to the point at which muscular function wheel-chair activity and limited self-help functional activities could be increased. Vital capacity had increased to 1.05 liters. The electrocardiogram during this period gradually reverted to the admission values. This example points up the importance of detecting the existence of cardiac disturbances in patients who do not have clinical evidence of cranial nuclear involvement. Onset of myocardial disturbances in the acute phase of the disease influenced the manner of resumption of activity in convalescence.

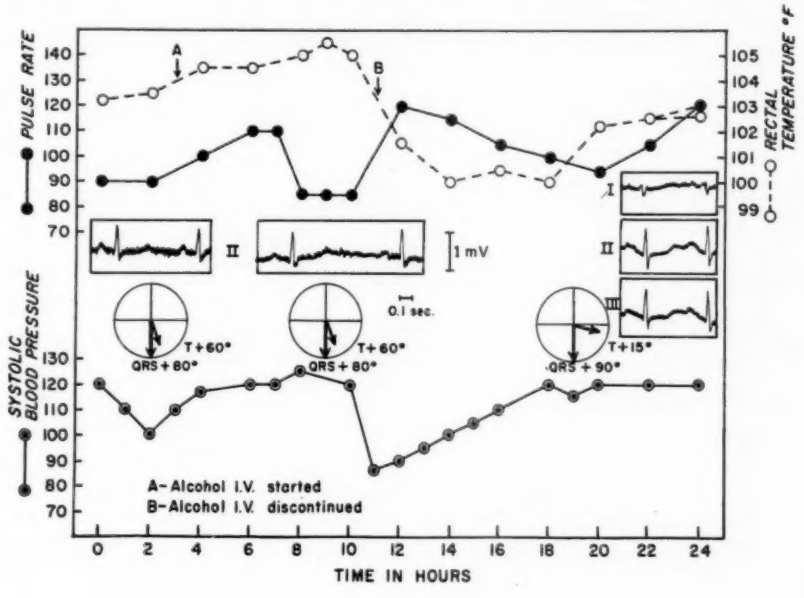

Fig. 6.—Pulse rate lability, bradycardia, and hyperthermia in spinal poliomyelitis with severe respiratory muscle paralysis. Pulse rate variations, systolic blood pressure, and body temperature are indicated in relation to the first 24 hours following hospital admission.

Fig. 7 illustrates the effect of a brief episode of arterial hypoxemia upon the pulse, blood pressure, and electrical activity of the heart in a 22-year-old clerk with severe swallowing difficulty and respiratory muscle paralysis requiring artificial respiration. This example was chosen to depict one genesis of pulse lability. Arterial oxygen unsaturation is associated with a rapid decrease in pulse rate and blood pressure in some poliomyelitis patients. Brief introduction of cuirass-respirator respiration in this apneic patient requiring constant respirator aid was the occasion of arterial oxygen unsaturation. At the time of these studies the patient was severely ill, febrile, and semicomatose. Respiratory management was judged to be adequate according to ventilatory measurements and arterial blood chemistry values. It can be seen that the arterial oxygen saturation on room-air breathing during tank-respiration (control period indicated at *O* on the abscissa of the graph, and *A* on the ECG record) was near normal at 92 per cent (direct sampling and Van Slyke manometric analysis of femoral arterial blood were employed for this series of measurements). Blood pressure was 125/90 mm. Hg at this time and *subsequently* at the 40-minute period when 100 per cent oxygen breathing was carried out. Oxygen saturation rose a little at this point. During the following period of room-air breathing, both in the tank- and cuirass-respirators, the patient's arterial oxygen saturation fell to 60 per cent, and the pulse rate rapidly declined to 80 per minute from the preceding rate of 120 to 130. Blood pressure, measured by auscultation and indirect cuff-sound registration, fell to 80 systolic, with diastolic pressure being unobtainable. Because of the pallor, sweating, and peripheral circulatory stasis noted during a trial period in the cuirass-respirator for nursing care, the patient was promptly returned to the tank-respirator and given 100 per cent oxygen in a closed system. The control values were not approximated

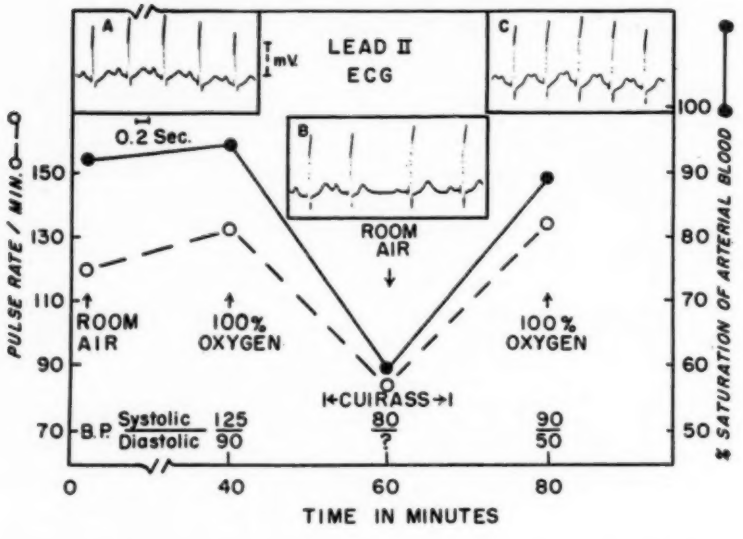

Fig. 7.—The genesis of bradycardia, hypotension, and cardioregulatory disturbances by hypoxemia in bulbospinal poliomyelitis. Percentage saturation of oxygen in femoral arterial blood is indicated on the right of the figure, and pulse rate values are shown on the left. Representative electrocardiograms *A*, *B*, and *C* coincide with 40, 60, and 80-minute time intervals. Equivalent ventilation volumes in both the tank and cuirass respirators were assured by spirometry. The patient was confined to the tank-respirator except for the period indicated *Cuirass*. Blood pressure values are indicated above the abscissa.

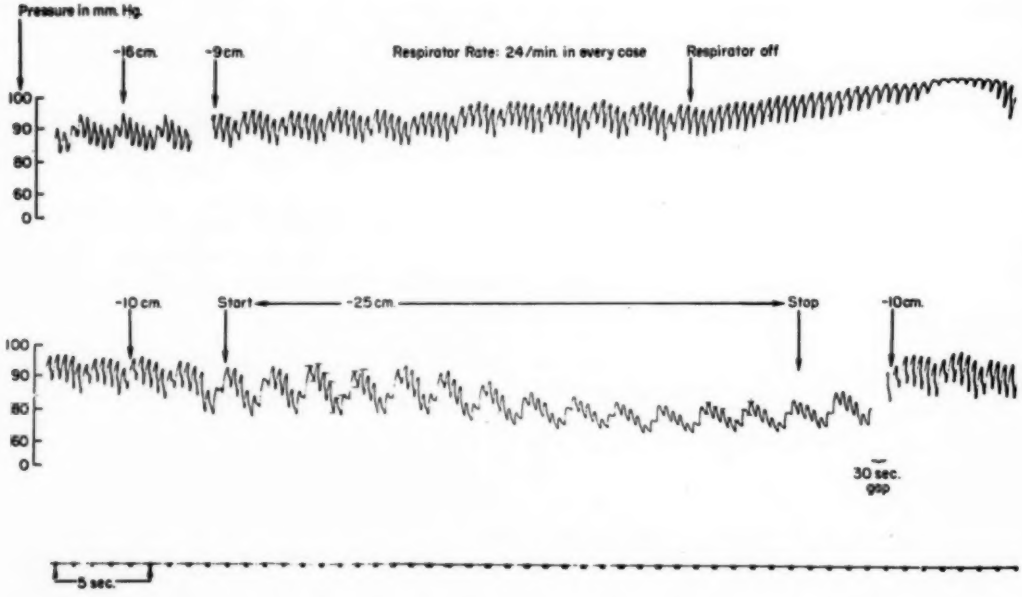

Fig. 8.—The effect of tank-respirator pressure breathing upon the femoral arterial blood pressure in a poliomyelitis patient with vasomotor incompetence. Sections of directly recorded femoral arterial blood pressure are indicated in relation to tank-respirator pressures and the cessation of artificial respiration. The blood pressure values are shown in relation to pressure calibration in millimeters of mercury on the ordinate at the left of the scale. Time calibrations are along the abscissa of the record and apply to upper and lower records except where gaps are indicated. Pulse pressure fluctuations are only to be considered representative and not true values because of the small caliber of the arterial needle.

except for oxygen saturation that increased to 90 per cent. In this instance, early use of the cuirass-respirator was not employed even though it could produce ventilation comparable to that achieved by the tank-respirator. The patient eventually recovered swallowing, cardioregulatory and vasomotor stability, and was weaned from the respirator. He is now functional and employed.

Fig. 8 shows the effect of tank-respirator respiration upon the femoral arterial blood pressure in a 7-year-old child with severe bulbar poliomyelitis and vasomotor incompetence. She had sufficient right diaphragm and intercostal paralysis to require constant artificial respiration, although she was able to breath unaided for brief periods. A tracheotomy was necessary to secure a patent airway and permit safe artificial respiration. She had evidence of vasomotor instability. This was followed by ECG evidence and auscultatory signs suggestive of myocardial insufficiency. Slight cardiac enlargement developed. She was desperately ill, and at the time the observation in this illustration was made, the patient had marked diminution in peripheral pulse volume during the cyclic excursions of the respirator. In view of this, direct femoral arterial blood pressure registration through a 22-gauge femoral needle was carried out. The record indicates that the respirator pressure of −16 cm. produced a greater decrease in mean blood pressure than did a pressure of −9 cm. Adequate pulmonary ventilation was obtained by more rapid cycling at the lower pressure. The respirator was turned off for a period of 2 minutes, and the blood pressure excursions of the femoral arterial pressure promptly rose. Following this, in a wave-like manner, the blood pressure declined and rose again. This peculiar lability was associated with alternate pallor and flushing of the skin. In the lower record the effect of a brief period of increased pressure of the magnitude of −25 cm. promptly produced a severe decline in the systemic blood pressure and pulse pressure. In all of these maneuvers, little variation in pulse rate was noted. Decrease of respirator pressure to −10 cm. permitted the re-establishment of the blood pressure at higher levels in approximately 30 seconds. Presumably the cardiac output improved in a similar manner. This illustrates the common variety of hypotension to be found during artificial respiration in poliomyelitis patients with some degree of vasomotor incompetence. The blood pressure was supported by norepinephrine during the first week of artificial respiration. The patient was subsequently weaned from all breathing aid, and swallowing returned. It was necessary to maintain strict bed rest, and to limit physical exertion of any type for a period of 3 months because of the persistence of myocarditis. Heart size, pulse rate, and the electrocardiogram eventually indicated a return to health, and the patient resumed her school and home activities.

SUMMARY

The frequency of clinically detectable cardiovascular abnormalities in the course of life-threatening poliomyelitis has been presented. The diagnostic criteria and recommended treatments for these conditions have been given. The description of circulatory complications was derived from experience with 1,490 acute poliomyelitis patients in a respirator center. A number of clinical examples of the pattern of disturbed function of nervous regulatory mechanisms, behavior of systemic and pulmonary circulation, and alterations of cardiac activity have been reviewed. Pathophysiologic changes in vital functions due to poliomyelitis complicated by respiratory insufficiency or swallowing difficulty have shown variability of timing and intensity. Experience indicates that careful and constant individualization in the planning and execution of preventive measures and treatment regimens is extremely important. Serial investigation of abnormal function affords guidance and knowledge that is particularly helpful in establishing definitive treatment and prognosis.

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Experimental and Laboratory Reports

The Effect of Reserpine and Digitalis on the Heart Rate During Noradrenaline Infusion

Gloria DeCarlo Massaro, M.D., Frank A. Finnerty, Jr., M.D., and Martin Ryan, M.D., Washington, D. C.*

Recent interest in this laboratory has centered around the response of the heart rate during noradrenaline-induced hypertension.[1,2] Since these studies demonstrated that most patients with clinical signs of arteriosclerosis exhibited a decreased bradycrotic response, it was postulated that the response of the heart rate during infusion of noradrenaline might be used as an index of arteriosclerosis. Patients who were receiving reserpine and/or digitalis were excluded from this study because of the possible interference of these agents with the bradycrotic response to noradrenaline. It was thought necessary, therefore, to determine whether these agents altered the response of the heart rate during infusion of noradrenaline. The present study was designed to evaluate the effect of reserpine and digitalis on noradrenaline-induced bradycardia.

METHODS AND MATERIALS

The patients were from the wards and clinics of the District of Columbia General Hospital. Twelve normal individuals without cardiovascular disease were studied. Eight were male and 4 were female. The average mean arterial pressure was 92 ± 9 mm. Hg. The average age was 26 (15 to 38) years.

The patients were in the fasting state and remained in the supine position throughout the procedure. Levarterenol bitartrate (Levophed) was administered as an intravenous infusion in a concentration of 4 μg/ml. of 5 per cent dextrose in water. The rate of infusion was regulated according to the decrease in heart rate and increase in arterial pressure, and varied between 3.2 and 6.4 μg/min. The end point of the experiment was taken as a decrease in heart rate of at least 13 per cent (10 beats per minute) or an increase in arterial pressure† of 25 per cent.

From the Department of Medicine, Georgetown University School of Medicine, and the Georgetown Medical Division of the District of Columbia General Hospital, Washington, D. C.

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†Arterial pressure = systolic + diastolic divided by 2.

TABLE I. THE RESPONSE OF THE HEART RATE AND ARTERIAL PRESSURE DURING INFUSION OF NORADRENALINE BEFORE AND AFTER RESERPINE + DIGITALIS

PATIENT	NORADRENALINE						DIGITALIS			RESERPINE		
	M.A.P.* (MM. Hg)		PER CENT INCREASE IN M.A.P.	HEART RATE (BEATS/MIN.)		PER CENT DECREASE IN HEART RATE	HEART RATE (BEATS/MIN.)		PER CENT DECREASE IN HEART RATE	HEART RATE (BEATS/MIN.)		PER CENT DECREASE IN HEART RATE
	BEFORE	DURING		BEFORE	DURING		BEFORE	DURING		BEFORE	DURING	
1.	83	95	14	66	56	15	66	72	↗6	—	—	—
2.	84	101	20	60	50	17	60	60	0	60	60	0
3.	95	105	11	80	64	20	80	68	15	—	—	—
4.	99	110	11	76	64	15	76	80	↗2	—	—	—
5.	90	105	17	56	46	18	56	56	0	56	56	0
6.	88	109	24	100	82	18	100	82	18	100	68	32
7.	95	104	10	74	62	16	—	—	—	74	60	19
8.	85	95	12	66	56	15	—	—	—	66	62	6
9.	110	138	25	76	66	13	—	—	—	76	64	16
10.	95	110	16	62	52	16	—	—	—	62	54	13
11.	100	130	30	90	66	27	—	—	—	90	86	4
12.	77	95	23	80	70	13	80	58	28	80	68	15
Average	92	108	18	74	61	17	74	68	9	74	64	12
Standard Deviation	±9	±13	±6	±13	±10	±4	±15	±10	±9	±14	±9	±8

TABLE I—CONT'D

PATIENT	NORADRENALINE + DIGITALIS						NORADRENALINE + RESERPINE					
	M.A.P. (MM. Hg)		PER CENT INCREASE IN M.A.P.	HEART RATE (BEATS/MIN.)		PER CENT DECREASE IN HEART RATE	M.A.P. (MM. Hg)		PER CENT INCREASE IN M.A.P.	HEART RATE (BEATS/MIN.)		PER CENT DECREASE IN HEART RATE
	BEFORE	DURING		BEFORE	DURING		BEFORE	DURING		BEFORE	DURING	
1.	82	100	22	72	60	17	—	—	—	—	—	—
2.	85	105	24	60	50	17	76	97	28	60	50	17
3.	100	117	17	68	52	24	—	—	—	—	—	—
4.	100	107	7	80	70	13	—	—	—	—	—	—
5.	89	105	19	56	46	18	80	97	21	56	46	18
6.	78	108	38	80	62	23	81	110	35	68	56	18
7.	—	—	—	—	—	—	80	98	23	60	52	13
8.	—	—	—	—	—	—	80	96	20	62	50	19
9.	—	—	—	—	—	—	112	136	22	64	54	16
10.	—	—	—	—	—	—	90	112	24	54	48	11
11.	—	—	—	—	—	—	100	132	32	86	60	30
12.	85	100	18	58	46	21	67	84	25	68	58	15
Average	88	106	21	68	55	19	85	107	26	64	53	17
Standard Deviation	±10	±6	±9	±10	±9	±3	±13	±17	±5	±9	±5	±5

*M.A.P. = mean arterial pressure = systolic + diastolic divided by 2.

Following these control studies, reserpine or digitalis therapy was initiated. Five patients received reserpine, 3 received digitalis, and 4 received reserpine plus digitalis. No patient received both drugs concomitantly. Reserpine was administered in a dosage of 2.5 mg. intramuscularly every 8 hours for 24 hours. Digitalization was accomplished by administering 0.1 Gm. of digitalis leaf three times a day for 4 days, then 0.1 Gm. daily for 14 days. Following the 24 hours of reserpine and the 17 days of digitalis, the noradrenaline test was repeated. The concentration and rate of infusion of noradrenaline were identical to the control levels.

RESULTS

The response of the heart rate and arterial pressure during infusion of noradrenaline before and after reserpine and digitalis can be seen in Table I. Under control conditions, infusion of noradrenaline was accompanied by at least a 13 per cent decrease in heart rate in all patients. Reserpine alone caused no change in heart rate in 2 patients, and an average decrease in heart rate of 15 per cent in the remaining 7 patients. Digitalis by itself caused no change in heart rate in 2 patients, an increase in heart rate of 4 per cent in 2 patients, and a reduction in heart rate of 20 per cent in the remaining 3 patients. It is interesting to note that the heart rate of the 2 patients which did not change during reserpine therapy also did not change following digitalis therapy. The reduction in heart rate following noradrenaline and reserpine and/or digitalis is not significantly different from the bradycardia following noradrenaline alone.

CONCLUSION

It would appear from these data that neither reserpine nor digitalis alters the response of the heart rate during infusion of noradrenaline.

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The Effects of Acetyl-Strophanthidin on the Kinetics of Potassium and Rb^{86} in the Myocardium of Dogs

A. B. Cairns, Jr., M.D., William D. Love, M.D., and George E. Burch, M.D.
New Orleans, La.

It has frequently been suggested that digitalis and similar drugs produce their characteristic effects on the heart by decreasing the myocardial concentration of potassium, or by changing the kinetics of potassium within the myocardium. Only the net shifts in ion produced by digitalis can be observed by the usual method, which is to measure the concentrations of electrolyte in the myocardium or in plasma collected from the coronary sinus following administration of the drug.

The observed changes in myocardial concentrations of potassium which occur immediately after the administration of digitalis could be produced by relatively small and minor changes in the rapid rates of exchange of potassium which normally exist in the heart muscle. On the other hand, these net shifts in ion might be but one manifestation of a more profound change in the kinetics of potassium within the myocardium. Isotopic tracers were employed in an attempt to determine the effects of a digitalis-like drug (acetyl-strophanthidin*) on the myocardial kinetics of potassium in dogs. Rb^{86} was employed as a qualitative and semiquantitative tracer of potassium because of its convenient half life of 18.7 days. This use is based on the general similarity of the chemical and biologic properties of rubidium and potassium, on the fact that these elements have comparable effects on the heart, and on data indicating the usefulness of Rb^{86} as a tracer of potassium in other biologic situations.[1-5]

MATERIALS AND METHODS

Dogs weighing 10.2 to 15.5 kilograms were anesthetized by the intravenous administration of 26 mg. of sodium pentobarbital per kilogram. The dogs received 100 mg. of heparin†. A flexible plastic cannula was guided through the right jugular vein into the coronary sinus a distance of approximately 2 to 3 centimeters by palpation through a right thoracotomy, while positive pressure

From the Department of Medicine, Tulane University School of Medicine, and the Charity Hospital of Louisiana, New Orleans, La.

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†Supplied by The Upjohn Company, Kalamazoo, Mich.

respiration was maintained with air. Samples were obtained volumetrically from this cannula in order to measure the coronary sinus outflow rates. Samples of blood were collected from the femoral artery simultaneously with those from the coronary sinus. Rb^{86} in 0.15M NaCl solution was administered in a peripheral vein at a continuously decreasing rate, as previously described, to maintain arterial levels of Rb^{86} approximately constant during the procedure.[5] Acetyl-strophanthidin in doses of from .038 to .075 mg. per kilogram was injected at times varying from 5 minutes before to 5 minutes after the start of the infusion of Rb^{86}. Control studies were obtained without drugs, with 0.7 to 1.0 mg. of nitroglycerin, or with 2 ml. of 29 per cent ethyl alcohol in water, the vehicle in which the acetyl-strophanthidin was administered. Mean femoral arterial blood pressure was measured with a mercury manometer. The dogs were sacrificed by injection of 600 mg. of sodium pentobarbital.

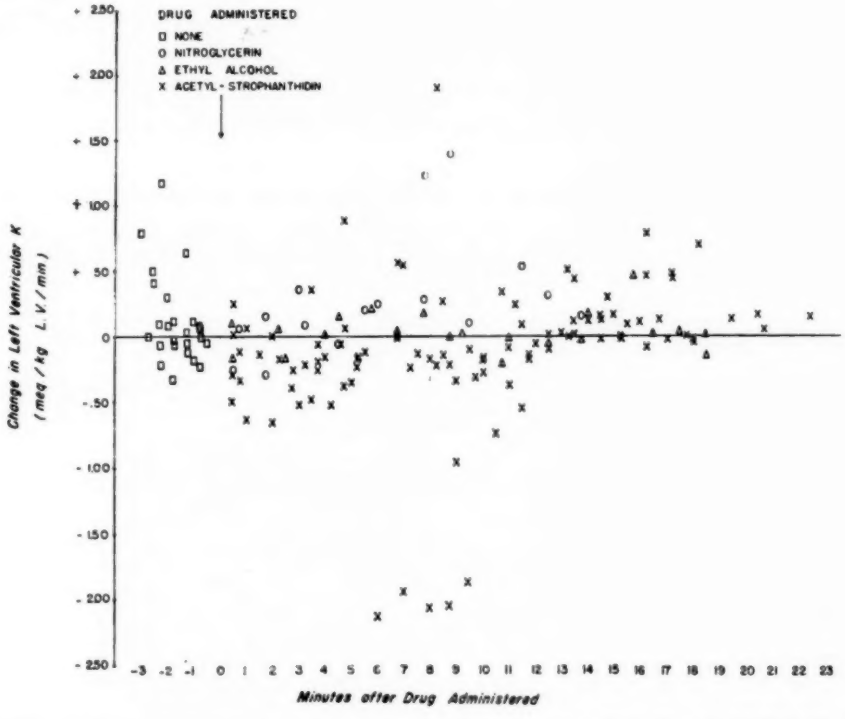

Fig. 1.—Changes in the concentration of potassium in the left ventricle in dogs receiving nitroglycerin, ethyl alcohol, or acetyl-strophanthidin.

The concentration of Rb^{86} in plasma was determined with end-window Geiger-Müller counters, as previously described.[6] The myocardial content of potassium and Rb^{86} was measured in three specimens from the left ventricle which were digested in nitric acid.[7] The values for each animal were averaged. Determinations of potassium were made with a Beckman DU flame spectrophotometer. The hematocrit was determined with a tube of 3-mm. bore and 10-cm. length, which was centrifuged for 45 minutes at a relative centrifugal force of approximately 2,000. Because the distance that the catheter was placed into the coronary sinus was not always the same, and because varying amounts of the left ventricle are drained by the coronary sinus,[8] the amount of the left ventricle drained by the catheter in each animal was calculated. This was done by utilizing the total amount of Rb^{86} extracted from the blood that flowed through the cannula and the final myocardial content of Rb^{86} measured at sacrifice. Using the Rb^{86}/K ratio in the myocardium at the time of sacrifice and the time course of the Rb^{86} uptake, the myocardial Rb^{86}/K ratio at the time of each sampling was calculated. The plasma flow per 100 grams of the left ventricle was found by relating the rate of blood flow from the cannula to the amount of left ventricle which it drained.[9]

RESULTS AND INTERPRETATION

One manifestation of the effect of acetyl-strophanthidin on the myocardial kinetics of potassium was the outpouring of potassium from heart muscle which occurred immediately after the drug was administered. Fig. 1 illustrates the changes in the myocardial concentration of potassium during the experimental procedure. These values were calculated from the rate of coronary plasma flow and the difference between the concentration of potassium in arterial plasma and that in coronary sinus plasma. Before administration of the drugs there was no significant net loss or gain of potassium by the myocardium. Within 1 minute after acetyl-strophanthidin was injected, the myocardium had begun to lose potassium at rates frequently ranging up to 0.65 mEq. of potassium per kilogram of left ventricle per minute. This effect disappeared within 12 minutes. In a single dog the rate of loss of potassium was three times this great for a period of several minutes. Nitroglycerin and ethyl alcohol produced no significant changes in the concentrations of potassium.

Any changes in the rates of exchange of potassium between the myocardial cell and the blood in the capillaries which might be produced by the administration of drugs should alter the degree of extraction of Rb^{86} from coronary plasma.

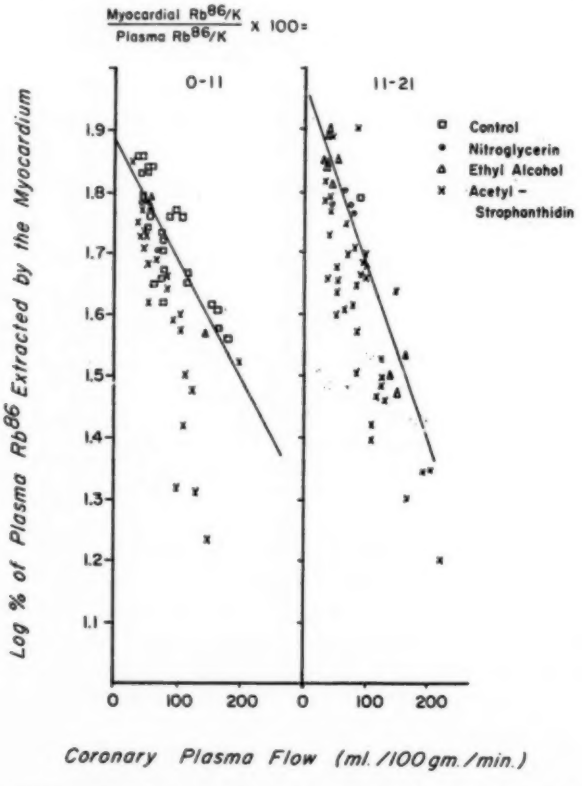

Fig. 2.—Effect of coronary plasma flow rate and of nitroglycerin, ethyl alcohol, and acetyl-strophanthidin on the extraction of Rb^{86} from coronary plasma in 15 dogs. Observations are subgrouped according to the myocardial content of Rb^{86} at the time of the measurement. Those in the column on the left were made when the Rb^{86}/K ratio within the myocardium was less than 11 per cent of that in the plasma. In those on the right this ratio ranged from 11 to 21 per cent. The plasma Rb^{86}/K ratio is essentially the same as that which would be present in the myocardium at equilibrium.

The experimental situation is affected by the fact that the degree of extraction of isotope is affected by the rate of coronary plasma flow.[9] Extraction is also related to the amount of isotope which has been accumulated by the myocardium, since the uptake of Rb^{86} behaves as an exchange process.[9,10] Therefore, the rate of coronary flow and the myocardial content of isotope have to be taken into account in evaluating the effects of drugs on the extraction of Rb^{86}. In the measurements made before the Rb^{86}/K ratio within the myocardium had risen to as much as one fifth of that in the plasma, there was less tracer extracted at all rates of coronary flow in the dogs that had received acetyl-strophanthidin (Fig. 2). All except 10 of these observations were made during the first 12 minutes after injection of this drug, which was the period of its peak action on the net exchange of potassium. In the 10 measurements made more than 12 minutes after the administration of acetyl-strophanthidin, there was no detectable reduction in the extraction of Rb^{86}.

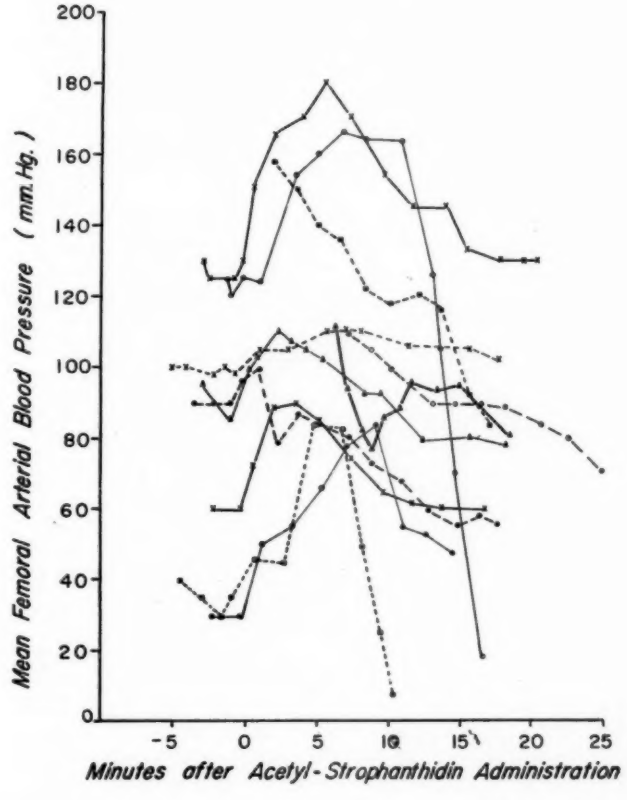

Fig. 3.—The effect of acetyl-strophanthidin on mean arterial blood pressure in dogs.

The effect of acetyl-strophanthidin on the extraction of Rb^{86} could have been mediated through some hemodynamic effect which caused changes in the capillary circulation. The effects of the drug on blood pressure and rates of coronary plasma flow are shown in Figs. 3 and 4. These changes indicate that significant hemodynamic effects occurred in these animals, although they do not indicate whether or not these had any direct effect on myocardial extraction of Rb^{86}.

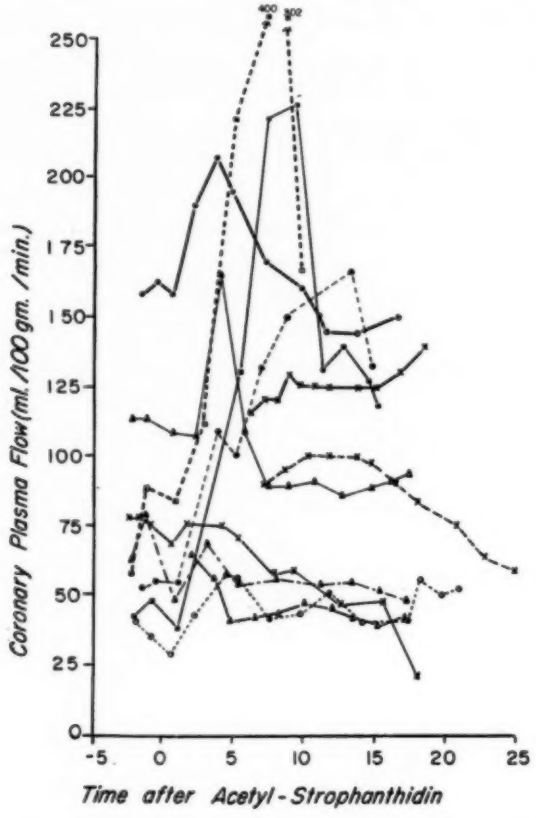

Fig. 4.—The effect of acetyl-strophanthidin on rates of coronary plasma flow in dogs.

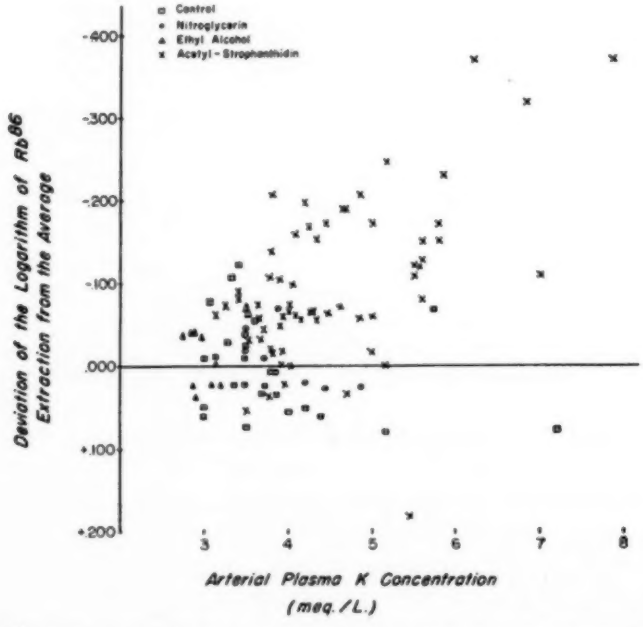

Fig. 5.—Relation of the concentration of potassium in plasma to the extraction of Rb^{86} by the myocardium of dogs. Extraction of Rb^{86} is expressed as a deviation from the average relationship shown in Fig. 2.

In 9 of 11 dogs the injection of acetyl-strophanthidin was followed by a rise in the concentration of potassium in arterial plasma. The greatest increase in the individual dogs ranged from 0.2 to 5.3 mEq./L. This change in the concentration of potassium in the plasma might have been responsible for the decline in the percentage of Rb^{86} extracted by the myocardium, but this seems unlikely since extraction decreased immediately after administration of the drug, before concentrations of potassium had risen significantly. No relation between the concentration of potassium and the extraction of Rb^{86} was noted in the range from 3.2 to 4.5 mEq. of potassium per liter of arterial plasma; yet in this range there was clearly less extraction from the plasma in the animals receiving acetyl-strophanthidin (Fig. 5).

Pulse rate has been mentioned as a possible determinant of the rates of myocardial exchange of potassium.[11] In these measurements, deviations of individual observations from the average relation of flow and extraction of Rb^{86} shown in Fig. 2 were not found to be related to the pulse rate at the time of the measurement (Fig. 6). It is possible that the relationships which have been noted between the exchange of isotope and the pulse rate or the individual mechanical systoles in an isolated perfused heart may have been caused by the intramyocardial mechanical mixing produced by the contraction, rather than by primary membrane phenomena.[12-14]

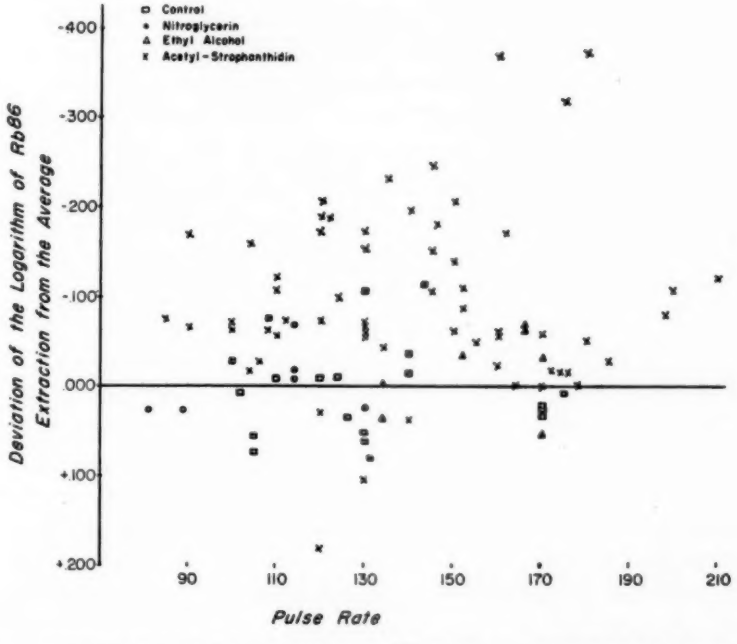

Fig. 6.—Relation of pulse rate and the extraction of Rb^{86} from coronary plasma in dogs. Extraction of Rb^{86} is recorded as a deviation from the average relationship shown in Fig. 2.

DISCUSSION

The effects of acetyl-strophanthidin on concentrations of potassium in arterial and coronary sinus plasma in this series of dogs were similar to those

reported by Regan, Talmers, and Hellems.[15] The measurements of coronary blood flow in the present study establish, in addition, the time course of the absolute amount of potassium lost by the myocardium. This loss averaged 0.25 mEq. per kilogram of left ventricle per minute during the period from 0.5 to 5.5 minutes after administration of the drug, as compared with simultaneous net changes in the controls.

The mean uptake of Rb^{86} from the coronary plasma in dogs receiving acetyl-strophanthidin was 41 per cent instead of the expected 51 per cent. The mean rate of coronary plasma flow in this group of observations after administration of acetyl-strophanthidin was 97 ml. per 100 Gm. of left ventricle per minute, and the concentration of potassium in arterial plasma averaged 4.6 mEq./L. If Rb^{86} traced potassium in this situation, the actual decrease in the amount of potassium entering the myocardium from the plasma was, therefore, 0.45 mEq. per kilogram of left ventricle per minute. This is almost twice as much as is needed to account for the decrease in myocardial content of potassium. The data therefore suggest that there was also a reduction in the amount of potassium passing out of the myocardium into the plasma. Although over-all myocardial uptake of potassium from the plasma can be measured by this technique, it is impossible to estimate accurately the decrease in the flux of potassium between myocardial cell and coronary capillary. However, if one assumes, on the basis of previous data,[9] that there is a functional arteriovenous shunting of 20 per cent of the coronary plasma within the myocardium at a coronary flow rate of 100 ml. of plasma per 100 Gm. of left ventricle per minute, calculations of membrane flux of potassium can be made. These show that the membrane flux of potassium would have to have decreased by 42 per cent in order to produce the fall in extraction of Rb^{86} found in the dogs receiving acetyl-strophanthidin, if the fall in extraction of isotope is to be accounted for on the basis of a change in transcapillary flux of ion. If, on the other hand, the reduction in extraction is due to hemodynamic changes, the amount of shunted plasma would have to have increased from 20 to 42 per cent of the total coronary flow.

Conn[11] reported that in dogs to which digitoxin was administered from 10 to 14 days the mean rate of transfer of potassium out of cells was reduced by 8 per cent, and the rate of transfer into the cells was reduced by 3 per cent. Burg and Orloff[16] have shown that in incubated slices of renal cortex, strophanthidin caused a diminution in the content of potassium by decreasing the influx of potassium, without any change in efflux. The changes which have been demonstrated in the flux of potassium between tissues and the circulating blood in this and other studies probably do not indicate the full effects of digitalis drugs on the cellular kinetics of potassium. The methods used would not detect changes in the intracellular kinetics of potassium, and such changes could be very great without affecting the exchanges of potassium with the extracellular environment.

SUMMARY

1. The kinetics of potassium in the dog myocardium were studied immediately following the administration of acetyl-strophanthidin, utilizing a Rb^{86}-tracer technique.

2. The immediate loss of potassium from the myocardium following administration of acetyl-strophanthidin averaged 0.25 mEq. per kilogram of left ventricle per minute.

3. The amount of tracer extracted from the blood by the myocardium declined immediately after the administration of acetyl-strophanthidin, indicating a reduction in the amount of potassium entering the myocardium from the plasma. There was probably a smaller reduction in the amount of potassium leaving the myocardium and entering the plasma, since the estimated decrease in the uptake of potassium was almost twice as much as the net loss of myocardial potassium. Calculations indicate that the decrease in the extraction of Rb^{86} by the myocardium after acetyl-strophanthidin could be explained by a fall of 42 per cent in the flux of potassium across the myocardial capillary or by a doubling of the amount of plasma functionally shunted past myocardial capillaries.

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The Effect of Hypoxia on the Rate at Which the Cardiac Ejection Force is Generated: A Ballistocardiographic Study

Arthur J. Moss, Lieutenant (MC) USNR, Pensacola, Fla.*

INTRODUCTION

For centuries the heart has been regarded as a pump, but only recently have some of its unique dynamic characteristics come under investigation. The total work done by the heart per cardiac stroke has always intrigued physicians. The external mechanical work of pressure-volume and flow performed by the heart is measurable, and it has been calculated previously.[1] This external work represents only a small fraction of the cardiac work load. Burton[2] has pointed out clearly that the internal static work of the heart, the so-called "tension and time" factor of isometric contraction, represents the major cardiac work load and requires the major fraction of oxygen consumption. Burch,[3] in a theoretical discussion of the human cardiac pump, showed that the load on the ventricles is greatest during isometric contraction and diminishes with ejection as the internal area of the heart rapidly declines. Even cardiac catheterization, with its direct entry into the cardiac chambers, has failed to elucidate the internal static factors, because the tension or force developed by the myocardial fibers has not been measurable.

Classically, the mechanical function performed by the heart is the rhythmic ejection of a bolus of blood at a changing acceleration under a pressure determined, in part, by the level of the peripheral resistance. Until quite recently, cardiac acceleratory and force factors could not be measured. In 1957, Reeves and associates[4] described an ultralow-frequency ballistocardiograph which measured the acceleration of the body produced by the recoil force of cardiac contraction and the impact forces of blood within the cardiovascular system. A typical acceleratory ballistocardiographic tracing similar to that described in the literature[5] is presented in Fig. 1. Reeves and associates[5] believe that the HI downstroke on the ballistocardiogram (BCG) was the most important representation of the acceleratory function of the left ventricle. It appears that a great deal of cardiac information can be obtained by closely examining the HI wave,† for it is

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*Research Associate, Cardiology Laboratory, U. S. Naval School of Aviation Medicine, Pensacola, Fla.

†The HI wave refers to the portion of the ballistocardiographic deflection between the H and I points.

produced by the cardiac recoil force. This force is transmitted to the body through the mediastinal structures, and it is considerably damped before it is recorded on the BCG as the HI downstroke. Nevertheless, the configuration of the HI wave reveals instant-to-instant dynamic events during the initial phase of cardiac ejection. The slope of the HI wave succinctly reveals acceleration per unit time, and it therefore reflects the rate at which cardiac ejection forces are generated.

Darby and associates[6] have recently pointed out that the acceleratory force of the ejected mass of blood is influenced both by the level of the peripheral resistance and the intrinsic contractile force of the myocardium. The rate at which the force inherent in the ejected blood is generated should reveal additional information about these variables and should reflect some information about the rate at which the contractile force is developed. One has the right to expect that the rate of change of the contractile force is related to the expenditure of the heart's energy per unit time, and thus indirectly to the cardiac load. Therefore, the rate at which the cardiac ejection force is generated, an expression obtainable from the slope of the HI wave of the BCG, reflects indirectly part of the cardiac load as well as the level of peripheral resistance.

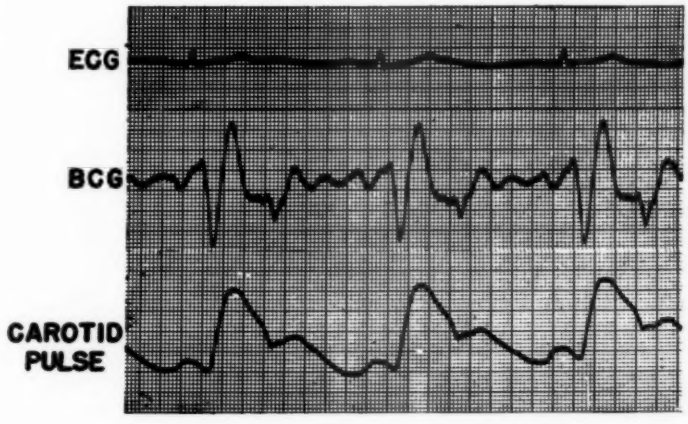

Fig. 1.—Simultaneous ECG, BCG, and carotid pulse tracing demonstrating the timing relationships between electrical and mechanical events in the cardiovascular system.

The purpose of the present experiment was to study in some detail the ballistocardiographic changes that take place in the HI wave and, more specifically, in the HI slope during a standard hypoxic stress to a group of normal subjects. It was hoped that the HI-wave changes with hypoxia would reveal additional information about cardiac dynamics.

PROCEDURE

Apparatus.—The ballistocardiograph used was an ultralow-frequency model described by Reeves, Jones, and Hefner,[4,5] and modified slightly as previously reported from this laboratory by Malt.[7] The bed platform was made of honeycomb aluminum and suspended by three 3/64-inch twisted seven-strand stainless steel cables. The mass of the table was 17 pounds and had a natural

frequency of 0.42 cycle per second. Acceleration was sensed only in the head-foot axis by an electronic accelerometer* which gave recordings comparable to the electrokinetic device of Elliott, Packard, and Kyrazis.[8] Lead II of the electrocardiogram (ECG) and the carotid pressure pulse (Infraton pulse wave recorder) were recorded simultaneously with the BCG on a Sanborn Poly-Viso recorder. The paper speed was 50 mm./sec. Sensitivity of the Sanborn apparatus was adjusted so that when about 300,000 dynes were applied by a pendulum to the bed loaded with 100 pounds, a 12.5 mm. deflection of the stylus was obtained. The polarity of the accelerometer was set up so that a headward acceleration produced an upward deflection of the recording stylus; a footward acceleration caused a downward deflection. The frequency response of the entire system was flat from 1 to 25 cycles per second and usable to 40 cycles per second. The patients were coupled to the bed through the use of a footboard, and by shoulder, chest, and waist straps.

Subjects.—The subjects used were 6 healthy male volunteers, aged 18 to 30 years. Before entering into the anoxic experiment, each subject at rest had a ECG which was interpreted as normal. The age, height, weight, ideal weight, and mean frontal QRS and T axes of the ECG are recorded in Table I. All 6 subjects had normal hemoglobins.

TABLE I. VITAL STATISTICS OF 6 EXPERIMENTAL SUBJECTS

SUBJECT NUMBER	AGE (YEARS)	HEIGHT (INCHES)	WEIGHT (POUNDS)	IDEAL WEIGHT* (POUNDS)	AXIS	
					QRS	T
1.	18	70	165	153–164	60°	60°
2.	20	73	165	166–178	75°	60°
3.	22	68	188	145–156	30°	30°
4.	23	69	167	149–160	0°	30°
5.	18	72	150	161–173	90°	75°
6.	30	70	210	153–164	30°	30°

*Ideal weight values were obtained from standard Metropolitan Life Insurance Company weight charts for individuals of medium frame.

Method.—Each of the 6 subjects was permitted to rest on the ballistocardiographic bed for a period of 15 minutes, during which time the recorded functions became stable. The subjects were then given 100 per cent oxygen by mask for 5 minutes—hereafter called the basal or resting period. Then, while the mask was still attached to the subject's face, the inhaled gas was changed to 10 per cent oxygen† for a period of 20 minutes. Thereafter, the subjects were given 100 per cent oxygen for a 5-minute recovery period. The BCG, blood pressure, and respiratory rate were recorded at the second and fifth minutes of the basal 100 per cent oxygen period; during the anoxic period,‡ records were made at minute intervals for the first 10 minutes, and then at 15, 16, 19, and 20 minutes of anoxia; during the 100 per cent oxygen recovery period, records were made at 1-minute intervals. Ballistocardiographic records during the basal, anoxic, and recovery periods were all taken with the subject in the held-mid-expiratory phase of respiration.

Analysis.—The BCG was inspected closely for changes in pattern during the anoxic and recovery periods as compared with the basal level. The following measurements were made from the ballistocardiographic trace, where Q refers to the initial ventricular depolarization on the simultaneous ECG, and H, I, and Jp (J peak) notations are standard nomenclature for the BCG waves[8]:

*Northam Accelerometer, Model A-14. Northam Electronics, Inc., Altadena, Calif.

†The gas mixture contained 10 per cent oxygen, 90 per cent nitrogen, and was accurate to ±0.5 per cent.

‡Anoxia and hypoxia will be used interchangeably throughout the rest of this paper when reference is made to the 10 per cent oxygen period.

1. *Q–H:* Time duration measured to the nearest 0.01 second from onset of ventricular depolarization to recorded H wave on BCG.

2. *Q–Jp:* Time duration measured to the nearest 0.01 second from onset of ventricular depolarization to recorded J peak on BCG.

3. *H–I:* Time duration measured to the nearest 0.01 second from H point to I point.

4. *HI amplitude:* Total vertical amplitude measured to the nearest 0.5 millimeter from H point to I point.

5. *HI angle:* A straight line is drawn through the H and I points, and the angle which this HI line makes with a true vertical on the ballistocardiographic paper is determined to the nearest 0.5 degree. Tangent and cotangent values for this angle can be obtained from trigonometric tables. The slope of this line closely approximates the slope of the true HI wave, for the latter is generally a straight line or nearly a straight line (see Fig. 2).

6. *IJ amplitude:* Total vertical amplitude measured to the nearest 0.5 millimeter from I point to J point.

7. *HR:* Heart rate obtained from the electrocardiographic trace.

The foregoing measurements were made on five consecutive complexes for each time interval recorded, and then averaged. It should be noted that visible measurements on the ballistocardiographic paper could be read accurately to the nearest 0.5 mm.

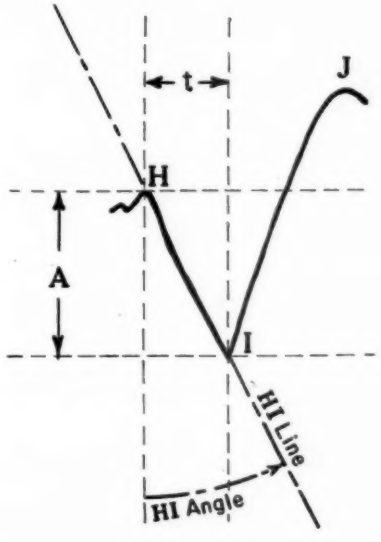

Fig. 2.—Enlargement of the initial part of the BCG, showing the details of the HI wave. *A* is the amplitude and *t* the time duration of the HI wave. The *HI Line* is drawn through the *H* and *I* points and closely approximates the slope of the HI wave. The *HI Angle* is measured from a true vertical passing through the *HI Line*.

RESULTS

The raw data obtained from the BCG of the 6 experimental subjects during the inhalation of 100 per cent oxygen and 10 per cent oxygen are presented in Table II. Each measurement recorded therein reflects the average value for the time interval specified. Each case showed a gradual increase in the heart rate during the anoxic stress. Blood pressures remained relatively stable, but tended to show slight elevation of the systolic pressures and variable depression of the diastolic levels over the initial basal 100 per cent oxygen states. In the ballistocardiographic recordings there were consistent increases in the amplitudes of the HI and IJ waves in all cases during the 10 per cent oxygen period as compared

TABLE II. BALLISTOCARDIOGRAM CHANGES WITH ANOXIA

	100% OXYGEN		10% OXYGEN														100% OXYGEN				
	MINUTES																				
	2	5	1	2	3	4	5	6	7	8	9	10	15	16	19	20	1	2	3	4	5
Subject 1																					
Q-H (sec.)	.08	.08	.08	.07	.07	.07	.07	.07	.08	.07	.08	.07	.07	.07	.07	.08	.06	.06	.07	.08	.07
H-I (sec.)	.08	.07	.07	.08	.08	.07	.08	.08	.07	.08	.07	.07	.07	.07	.07	.06	.08	.08	.08	.08	.07
HI (mm.)	12.5	11.7	11.5	12.0	12.2	11.0	13.0	11.7	13.1	13.5	10.3	14.6	12.1	12.6	14.7	14.3	13.5	13.7	12.7	12.3	11.8
HI angle	15.9	16.8	16.0	17.8	18.3	17.6	16.4	16.7	15.0	14.8	17.7	12.8	15.9	15.2	12.5	13.1	15.9	15.0	16.8	16.1	17.1
Cot. HI	3.55	3.31	3.48	3.12	3.02	3.15	3.40	3.33	3.73	3.78	3.13	4.40	3.51	3.68	4.51	4.30	3.51	3.73	3.40	3.46	3.25
IJ (mm.)	24.6	22.2	23.6	23.4	22.2	22.8	23.8	22.8	23.8	23.2	22.0	25.0	25.4	26.4	26.6	26.0	26.2	26.0	23.8	25.4	24.8
Q-Jp (sec.)	.22	.22	.22	.22	.23	.23	.22	.22	.22	.22	.22	.22	.22	.22	.22	.21	.22	.22	.22	.22	.22
B.P.	124/88	126/86	130/84	130/82	130/88	138/90	130/80	130/84	124/82	130/82	132/86	132/90	130/84	130/84	134/80	130/82	122/90	130/90	120/90	124/88	130/90
H.R.	64	67	65	71	74	72	72	71	73	74	68	77	71	68	77	77	68	66	63	61	63
Resp.	14	12	12	12	12	14	16	12	14	14	12	14	14	12	14	12	12	12	16	12	14
Subject 2																					
Q-H (sec.)	.05	.05	.05	.05	.05	.04	.04	.05	.05	.03	.04	.05	.05	.05	.05	.05	.05	.04	.04	.05	.05
H-I (sec.)	.08	.07	.07	.08	.07	.07	.07	.07	.07	.08	.07	.07	.07	.07	.07	.06	.08	.09	.09	.08	.08
HI (mm.)	12.0	11.4	11.5	13.8	12.1	12.3	12.9	13.0	11.8	13.5	12.5	13.0	14.7	13.5	12.5	12.3	12.7	11.1	9.8	6.7	7.4
HI angle	19.0	19.1	18.2	15.6	16.1	16.2	15.5	15.2	16.3	16.0	15.0	15.0	12.9	13.9	13.8	13.8	17.6	21.6	23.0	24.9	24.6
Cot. HI	2.90	2.89	3.04	3.58	3.46	3.44	3.60	3.68	3.42	3.49	3.73	3.73	4.37	4.04	4.07	4.07	3.15	2.53	2.36	2.15	2.18
IJ (mm.)	21.6	20.4	20.4	23.4	19.5	21.4	22.2	23.2	23.0	24.0	23.4	24.0	26.4	26.4	25.0	25.6	23.0	20.6	21.0	17.4	16.8
Q-Jp (sec.)	.22	.22	.22	.22	.22	.23	.22	.23	.22	.22	.22	.20	.22	.22	.24	.23	.22	.23	.24	.24	.23
B.P.	98/60	100/60	108/60	118/70	120/68	128/70	124/70	120/68	122/68	122/62	120/64	130/70	120/60	130/58	112/68	120/58	112/64	110/68	110/70	120/70	120/68
H.R.	55	54	55	64	70	74	75	80	81	76	78	80	81	80	83	82	54	52	49	48	48
Resp.	10	10	10	8	8	8	10	8	10	10	8	10	10	10	10	10	10	10	10	10	10
Subject 3																					
Q-H (sec.)	.09	.10	.10	.10	.10	.10	.10	.09	.08	.10	.10	.10	.10	.10	.10	.11	.11	.10	.10	.10	.10
H-I (sec.)	.07	.06	.07	.07	.06	.07	.06	.07	.09	.07	.07	.07	.07	.06	.06	.06	.07	.08	.07	.08	.08
HI (mm.)	5.3	4.8	4.9	5.9	5.6	9.8	6.3	9.2	8.0	8.1	6.6	9.9	9.0	7.2	7.4	7.9	6.1	5.6	5.0	6.0	5.4
HI angle	30.4	30.8	32.3	27.0	24.0	17.9	23.6	21.0	24.1	20.8	22.7	17.1	18.8	19.8	20.3	18.3	26.5	27.6	30.0	27.9	29.6
Cot. HI	1.70	1.68	1.58	1.96	2.25	3.09	2.29	2.60	2.24	2.63	2.39	3.25	2.94	2.78	2.70	3.02	2.00	1.91	1.73	1.89	1.76
IJ (mm.)	12.0	12.0	11.4	13.4	14.8	16.2	12.8	15.4	12.8	14.4	12.6	15.8	15.2	15.2	14.8	16.0	11.8	10.6	9.6	10.0	9.8
Q-Jp (sec.)	.26	.26	.26	.26	.25	.26	.26	.26	.26	.26	.26	.26	.26	.26	.26	.26	.28	.27	.29	.28	.29
B.P.	120/70	124/70	120/70	126/70	130/68	130/70	130/68	124/64	120/68	120/62	114/60	112/62	108/64	114/62	114/60	116/64	102/70	102/72	112/72	110/70	120/70
H.R.	51	51	53	64	70	80	83	80	76	81	86	78	80	65	70	63	47	46	44	47	45
Resp.	12	12	12	10	10	10	12	12	12	12	12	12	10	10	12	12	12	12	10	12	12

Subject 4																					
Q-H (sec.)	.12	.12	.12	.12	.12	.12	.12	.12	.12	.12	.12	.12	.12	.12	.12	.12	.12	.12	.13	.13	.11
H-I (sec.)	.06	.06	.06	.06	.05	.06	.04	.05	.06	.05	.04	.05	.05	.04	.04	.05	.05	.06	.06	.06	.05
HI (mm.)	10.2	9.9	9.8	10.2	9.9	10.3	12.2	10.4	12.2	11.5	11.8	11.9	12.7	12.3	13.7	13.0	10.2	11.6	9.3	10.3	11.0
HI angle	14.9	15.2	14.8	13.9	14.3	13.9	8.5	11.7	12.2	11.2	10.8	11.8	11.4	8.6	7.3	10.3	13.9	13.0	16.5	15.9	14.1
Cot. HI	3.76	3.68	3.78	4.04	3.92	4.04	6.69	4.83	4.63	5.05	5.24	4.79	4.96	6.46	7.80	5.50	4.04	4.33	3.38	3.51	3.98
IJ (mm.)	19.2	18.2	20.0	21.0	20.2	20.6	25.2	22.8	23.4	22.4	23.4	22.2	23.6	23.5	27.2	23.8	19.8	21.2	17.4	20.0	21.0
Q-Jp (sec.)	.28	.28	.28	.28	.27	.26	.25	.27	.28	.26	.26	.28	.27	.24	.25	.26	.26	.26	.28	.26	.27
B.P.	92/70	90/70	102/70	100/64	110/68	96/70	110/70	102/68	98/68	100/70	100/68	92/68	96/70	96/70	108/70	104/72	98/70	92/74	102/78	94/74	90/70
H.R.	55	53	54	63	58	59	65	65	67	63	65	68	67	61	67	69	54	52	51	52	53
Resp.	16	16	14	16	16	16	16	16	16	14	14	16	12	14	14	16	10	10	12	12	12
Subject 5																					
Q-H (sec.)	.10	.10	.10	.10	.10	.10	.10	.09	.10	.09	*	.09	.10	.10	.10	.10	.10	.10	.10	.10	.10
H-I (sec.)	.04	.03	.03	.03	.03	.03	.03	.03	.03	.03	*	.03	.03	.02	.03	.03	.03	.03	.04	.04	.03
HI (mm.)	8.9	9.8	10.1	13.4	13.6	11.6	12.9	11.5	11.1	11.0	*	13.1	11.1	12.2	11.5	11.7	9.5	8.7	10.1	8.8	7.6
HI angle	10.5	8.2	8.5	6.6	6.9	7.1	7.0	7.6	7.8	7.3	*	7.1	8.0	5.7	6.9	6.3	8.9	11.1	9.5	10.5	10.7
Cot. HI	5.40	6.94	6.69	8.64	8.26	8.03	8.14	7.49	7.30	7.81	*	8.03	7.12	10.02	8.26	9.06	6.39	5.10	5.98	5.40	5.29
IJ (mm.)	18.4	18.2	20.0	23.6	24.6	22.6	23.2	22.4	22.8	21.4	*	27.6	23.2	22.2	22.2	24.0	20.0	18.0	19.4	16.8	16.9
Q-Jp (sec.)	.24	.22	.22	.22	.22	.22	.22	.21	.22	.21	*	.21	.22	.21	.22	.22	.23	.22	.23	.22	.23
B.P.	114/70	112/70	106/70	110/70	108/70	110/64	112/66	108/66	110/66	110/68	*	120/60	110/58	110/64	120/60	112/60	112/76	104/74	108/78	110/76	112/78
H.R.	75	71	75	85	83	86	90	88	86	87	*	79	83	88	85	90	70	67	66	65	68
Resp.	16	16	16	16	16	16	16	16	16	16	*	16	16	20	16	16	16	16	16	16	16
Subject 6																					
Q-H (sec.)	.08	.08	.08	.08	.08	.08	.08	.08	.08	.08	.08	.08	.08	.08	.08	.08	.08	.08	*	.08	.08
H-I (sec.)	.06	.06	.04	.04	.04	.04	.04	.04	.04	.04	.04	.04	.04	.04	.04	.04	.04	.04	*	.05	.06
HI (mm.)	9.4	9.0	9.2	10.5	12.4	12.1	11.8	10.9	13.4	14.2	12.9	18.1	18.9	18.6	18.7	17.5	7.6	8.7	*	10.7	7.5
HI angle	17.0	18.3	13.2	10.6	10.1	9.1	8.4	8.2	7.1	7.2	7.2	6.1	6.0	6.1	5.7	6.1	14.5	14.0	*	13.7	20.8
Cot. HI	3.27	3.02	4.26	5.34	5.61	6.24	6.77	6.94	8.03	7.92	7.92	9.36	9.51	9.36	10.19	9.36	3.87	4.01	*	4.10	2.63
IJ (mm.)	10.8	10.5	11.2	13.8	15.4	14.4	13.4	12.6	14.2	15.6	16.0	18.4	20.2	20.4	20.6	21.2	9.8	10.0	*	11.4	9.2
Q-Jp (sec.)	.22	.22	.24	.22	.20	.23	.22	.23	.23	.20	.20	.20	.20	.20	.20	.20	.20	.20	*	.21	.22
B.P.	103/84	106/86	112/88	118/88	118/86	116/82	118/84	118/82	120/80	118/78	118/76	118/78	118/72	120/74	110/70	114/70	112/84	108/82	*	110/84	104/82
H.R.	63	63	71	74	78	81	80	83	81	82	86	80	79	79	79	78	70	63	*	62	62
Resp.	14	14	12	14	14	16	14	14	12	14	12	12	12	12	12	12	12	10	*	12	14

***Indicates time intervals when no data were recorded because of technical difficulties.**

with the basal state. The duration of time from H to I points (H-I) shortened measurably in some cases (Subjects 1, 4, 6), by 0.01 to 0.02 second, during the anoxia. In all cases the HI angle became more acute during the anoxia and rapidly returned to about that of the basal state when the patients were once again given 100 per cent oxygen.

It is interesting to note that the amplitude of the HI wave and the size of the HI angle varied considerably from one subject to another in the resting state. The HI angle in the resting state ranged from 30.6° in Subject 3 to 9.4° in Subject 5. However, for each experimental subject there was relatively small variance in the five measurements of the HI angle during the resting state—the range being 0.1° to 2.3°.

As described in the introductory paragraphs, the rate at which the cardiac acceleratory force is generated is reflected in the slope of the HI wave. The slope of the HI wave, assuming it to be a straight line, can be calculated from the cotangent to the HI angle, and the value obtained represents acceleration/time. Since the HI angle became more acute in all of our subjects during the anoxic stress, the cotangent HI must increase as a trigonometric function of the changing angle.

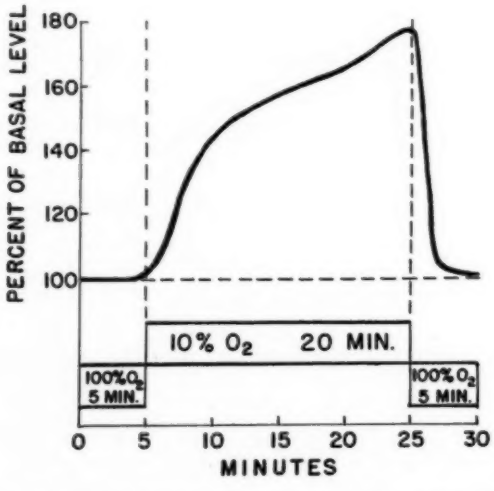

Fig. 3.—A graph obtained from the average data for each time interval in Table IV. The vertical axis records the average percentage alteration of the basal rate of cardiac ejection. The basal rate is assumed to be at 100 per cent. The horizontal axis records the time in minutes during the 100 per cent and 10 per cent oxygen periods. During the anoxia the average rate of cardiac ejection increases to a level of 176.7 per cent of the basal rate, and then quickly returns to the basal level during the recovery period.

For each experimental subject an average value for the cotangent HI angle during the initial 100 per cent oxygen period was assumed to represent the basal rate of cardiac ejection. This basal value was used in subsequent calculations as a reference level, and for each individual it was considered to be the 100 per cent resting value. Average values for the percentage of the basal rate of cardiac ejection were then obtained for the 1-5 minute, 6-10 minute, 15-16 minute, and 19-20 minute periods of 10 per cent oxygen as well as for the interval of 100 per cent oxygen immediately following the anoxia. These results are recorded in

Table III. It should be noted that in the calculation of the percentage alteration of the basal rate of cardiac ejection, the percentage alterations in the rate of cardiac acceleration and in the rate of cardiac force generated (Force/time) are interchangeable.*

It is clearly evident from Table III that the rate at which cardiac ejection force was generated was significantly increased in every subject during the anoxic stress period. These data reflect the fact that the HI angle became more acute with anoxia (Table II). Fig. 3 is a summary plot of the average percentage increase in the rate of cardiac ejection for each time interval in Table III. The graph succinctly reflects the increase in the rate of cardiac ejection with anoxia and the rapid return toward normal during the recovery period.

TABLE III. THE PERCENTAGE ALTERATION OF THE BASAL RATE OF CARDIAC EJECTION FORCE OBTAINED DURING ANOXIC AND RECOVERY PERIODS

SUBJECT	100% OXYGEN	10% OXYGEN				100% OXYGEN
	5 MIN. (%)	1-5 MIN. (%)	6-10 MIN. (%)	15-16 MIN. (%)	19-20 MIN. (%)	5 MIN. (%)
1.	100.0	94.9	107.7	104.0	129.2*	101.2
2.	100.0	118.1*	124.1*	145.0*	140.4*	85.8*
3.	100.0	132.4*	155.2*	169.3*	169.3*	109.9*
4.	100.0	120.6*	132.0*	156.3*	178.9*	103.3
5.	100.0	129.2*	124.2*	138.2*	132.3*	91.3
6.	100.0	178.1*	254.8*	299.2*	310.1*	115.3*

*Indicates a significant change from the basal level at a p value of less than .05.

The increase in the time rate of change of the cardiac ejection force with anoxia (Force/time) may reflect an absolute increase in cardiac force per se, or a decrease in the time interval during which ejection has taken place, or a combination of these two factors. It is important to know the degree to which each factor is being changed by the anoxia. An absolute increase in cardiac ejection force alone during anoxia would produce a more acute HI angle as a result of an increase in the HI amplitude, but there would be no change in the H-I time interval. Similarly, the heart may generate the same cardiac force during anoxia as during the basal state but deliver it in a shorter period of time. In this case, the HI angle would become more acute as a result of a diminution in the H-I time duration; the HI amplitude would remain unchanged. If both cardiac ejection force were increased and ejection time decreased, then not only would the HI amplitude increase, but, also, the H-I time interval would shorten. It is evident that changes in the HI amplitude and H-I time duration reflect, respectively, the changes in centrally generated cardiac acceleratory force and concomitant ejection time so long as the HI wave is a straight line. It should

*Force/time = Mass × acceleration/time. Upon calculation of the percentage change of Force/time (F/t) for each individual the mass cancels out. Thus, the percentage change in F/t is the same as the percentage change in acceleration/time.

be remembered that the HI wave reflects only the very small initial fraction of the entire cardiac ejection, and the I point correlates with the maximum acceleration of the ejected blood.[5]

In Table IV are presented the percentage alterations of the basal HI amplitudes and H-I time durations during the resting state, the anoxia, and the oxygen recovery periods. The resting HI amplitude and H-I time were assumed to represent a 100 per cent basal level. A change in the amplitude or time value during the anoxic and recovery periods was compared with the value at basal level, and a percentage of the basal value obtained. The table reveals that for each subject there was a significant increase in HI amplitude (cardiac force) for at least one time interval during the anoxia. Also, 5 of the 6 subjects showed a significant decrease in the H-I time duration for at least one hypoxic time interval. Thus, alterations in both force and time factors generally were operating to give an increased rate of cardiac ejection during the stress of anoxia. The shortening of the H-I time is revealed qualitatively in the raw data in Table II, in which the directly measured H-I time durations showed a tendency to shorten for all subjects and were most marked and obvious in Subject 6. The H-I time intervals referred to in Table IV were obtained indirectly by calculation from the HI amplitudes and the tangents of the HI angles.* The changes in the H-I time were obtained more accurately by this indirect method than by direct observation, and small changes in H-I time could be calculated mathematically but not visibly ascertained.†

As can be seen from Table III, the increase in the rate at which the cardiac force was generated (Force/time) was somewhat variable from one individual to another during the anoxia. Five of the 6 subjects showed a significant increase within the first 5 minutes of the anoxia; one individual did not show a significant increase until the 19-20 minute period (Subject 1). Subject 6 had a comparatively exaggerated response during all periods of the anoxia, and at the 19-20 minute period he increased by 310.1 per cent of the basal resting state the rate at which he delivered his cardiac acceleratory force. This percentage increase was considerably greater than that manifested by any other experimental subject. Table IV shows the same variable pattern in the change of the HI amplitudes and the H-I time intervals. Once again the changes were most marked in Subject 6. When the anoxic period was ended, the record of this subject did not return readily to that of the basal state. Rather, his rate of cardiac ejection remained significantly elevated at 115.3 per cent of the basal level during the 100 per cent oxygen recovery period. This elevation principally reflected a persistent decrease in ejection time as revealed in Table IV. Subject 3, who also had a significant elevation in the rate of cardiac ejection during the recovery period, appeared to have had such an elevation primarily as a result of increased cardiac force rather than decreased ejection time. Slowness in the return to the basal level for these individuals may well have cardiac significance and will be commented

*Since the slope of the HI wave, the HI amplitude, and the H-I time duration form a right triangle, then: H-I duration = HI amplitude × tangent HI angle.

†See Discussion.

upon in the discussion section of this paper. Table III also reveals that Subject 2, in contrast to Subjects 3 and 6, obtained a significantly lower rate of cardiac ejection during the recovery period than during the initial basal resting state. Table IV indicates that this decrease in F/t for Subject 2 principally reflected a decrease in cardiac force per se, with the cardiac ejection time essentially the same as in the basal state.

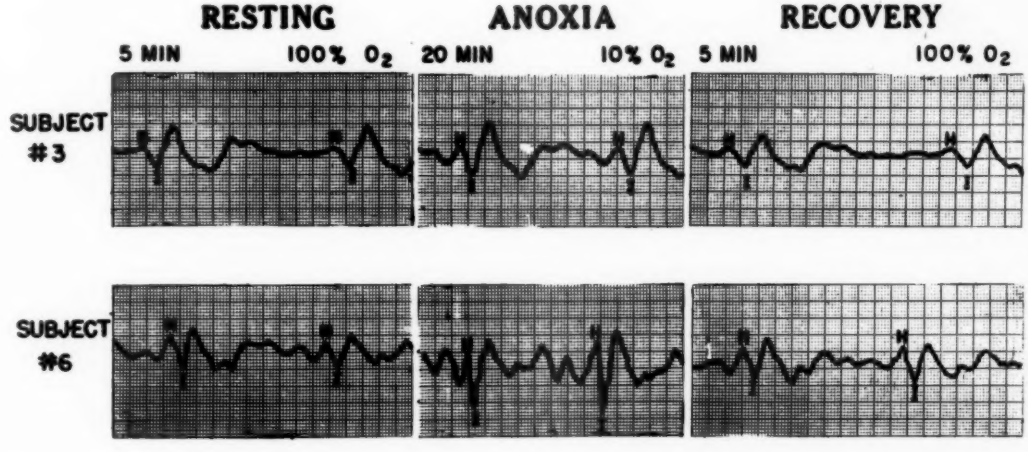

Fig. 4.—Representative BCG records from two subjects during resting, anoxia, and recovery periods. Note the more acute HI slope in each subject after 20 minutes with 10 per cent oxygen.

TABLE IV. THE PERCENTAGE ALTERATIONS OF THE BASAL CARDIAC EJECTION FORCE (HI AMPLITUDE) AND EJECTION TIME (H-I TIME) OBTAINED DURING ANOXIC AND RECOVERY PERIODS

SUBJECT	EJECTION	100% OXYGEN	10% OXYGEN				100% OXYGEN
		5 MIN. (%)	1-5 MIN. (%)	6-10 MIN. (%)	15-16 MIN. (%)	19-20 MIN. (%)	5 MIN. (%)
1.	HI Amp.	100.0	98.4	104.0	102.1	119.9*	105.8
	H-I Time	100.0	105.7	100.0	94.3	94.3*	105.7*
2.	HI Amp.	100.0	107.0*	110.8*	122.3*	106.0	81.6
	H-I Time	100.0	98.8*	87.8*	82.9*	75.6*	95.1
3.	HI Amp.	100.0	127.7*	164.5*	159.4*	150.5*	110.3*
	H-I Time	100.0	100.0	106.5	90.3	87.1*	96.8
4.	HI Amp.	100.0	103.8	114.5*	123.9*	132.4*	103.8
	H-I Time	100.0	88.9*	85.2*	85.2*	74.1*	100.0
5.	HI Amp.	100.0	131.5*	123.3*	124.1*	118.1*	95.1
	H-I Time	100.0	100.0	93.7	87.5	81.4	100.0
6.	HI Amp.	100.0	121.7*	151.1*	203.8*	196.8*	93.7
	H-I Time	100.0	75.9*	58.6*	72.4*	62.1*	82.8*

*Indicates a significant change from the basal level at a p value of less than .05.

In Fig. 4 are seen the actual ballistocardiographic tracings of 2 experimental subjects for representative periods during the resting, the anoxic, and the 100 per cent oxygen recovery periods. It is evident that the angle that the HI wave made with the vertical line became more acute during the anoxia.

TABLE V. CORRELATION COEFFICIENTS FOR THE PERCENTAGE INCREASE IN THE RATE OF CARDIAC EJECTION AT THE 19-20 MINUTE ANOXIC PERIOD

	RESTING HI AMP.	RESTING HI ANGLE	RESTING H.R.	PER CENT INCREASE IN H.R.
Per cent increase in F/t at the 19-20 min. anoxic period	−.24	.12	−.08	−.06

It would be valuable to know whether there is some way one could predict the change in F/t that occurs during anoxia from either the basal BCG, the resting heart rate, or the increase in the pulse seen with anoxia. A correlation coefficient table was therefore constructed for these variables from the data in Tables II and III, and the results are presented in Table V.

It is obvious from Table V that no significant correlations existed. Thus, the percentage increase in the rate at which cardiac force is generated during anoxia cannot be predicted from any of the standard measurements heretofore mentioned.

DISCUSSION

Meaning of Force/Time.—The slope of the HI wave became significantly more acute in each subject during the anoxia. As pointed out in the introduction, the HI slope is influenced by the rate of generation of the initial cardiac ejection force. The rate of change of force with respect to time (F/t) is not a frequently used physical concept. Power, the time rate of doing work (W/t), has wide application and is a standard reference in comparing engines and motors. It is obvious that F/t bears a close relationship to W/t; the only factor missing is distance, for Work = Force × Distance. The addition of a displacement measurement to an acceleratory BCG would then record sufficient information to obtain a relative measurement of heart power, a concept referred to by Starr[10] in his work with the high-frequency displacement BCG. Starr, in this same article, commented that the cardiac energy delivered to the blood per unit time determines in large part the genesis of the BCG, especially the early part. The rate of change of the ejection force bears a relationship to the expenditure of energy per unit time of the heart, and as pointed out in the introduction of this paper, it should reflect some information about the cardiac load.

The rate of change of force or acceleration has been referred to, and used, in other fields of medicine as well as in other disciplines. In aviation medicine, Stapp[11] and Bechman and associates[12] have studied human tolerance to accelerative stress. Stapp[11] demonstrated that at very high G rates, 500 to 1,500 G/sec., the greatest load tolerated by the entire organism did not occur during the maximal rate of application of the G stress, but rather during submaximal rates.

Stoll,[13] working with very low G rates, 0.2 to 8.0 G/sec., demonstrated that there is a greater time lag between grayout and unconsciousness at lower rates of acceleration than there is at higher rates. The explanation for this is that greater stress is applied in a shorter time at higher rates of acceleration. In the field of engineering, the rate of change of an applied force is referred to as "jerk," and it is one of the factors determining metal durability. A common example of this principle is seen when the force applied to bend a thin metal rod is rapidly changed to and fro. At the point of rapid bending the metal heats up, fatigues, and breaks. In electronics, the electrical generator has a maximum voltage which it can produce in a given period of time. If the generator is called upon to increase beyond its maximum limit, the rate at which it generates voltage, it is likely to burn itself out. From these examples it can be seen that the load upon an entire human organism, a metal rod, or an electrical generator is determined in part by the rate of change of acceleration or force, applied or generated. Similarly, for the human heart it seems reasonable that part of the cardiac load is reflected in the rate at which cardiac contractile force is developed. As pointed out earlier, the rate of change of the contractile force is represented in the rate at which cardiac ejection force is generated. This latter quantity is determined easily from the HI slope on the BCG.

Physiologic Effects of Hypoxia on the HI Wave.—In the present experiment the stress applied to evoke a cardiac response was the standard 10 per cent oxygen test. Since the subjects were all young, normal, healthy individuals, the arterial oxygen saturation at the end of 20 minutes was assumed to be essentially the same for all the individuals, about 73 to 75 per cent.[14] Oximeter evaluation of the level of arterial desaturation was not done, and it is possible that there could have been significant individual variation, as pointed out by Tewell and Pritchard.[15] Thus, to quantitate truly each individual's response and compare the change in the HI slope among individuals, specific arterial oxygen saturation levels must be known. Such information was not quantitatively necessary in the present experiment, for only qualitative results are being reported, i.e., during anoxia there was a general increase in the rate at which cardiac ejection force was generated.

The physiologic effects of anoxia on the cardiovascular–pulmonary system in the normal healthy individual are quite well known[16-19] and may be somewhat variable in different subjects.[20] The responses to anoxia included the development of hyperventilation, mostly caused by an increased depth of respiration; the arterial carbon-dioxide tension becomes secondarily lowered; there is an increase in the heart rate and cardiac output; the stroke volume remains constant or increases only slightly; the systolic blood pressure remains generally unchanged; and there is a slight fall in diastolic pressure. Hellems and associates[19] showed that the total peripheral resistance decreased during hypoxia, there was a slight yet nonsignificant increase in left ventricular work, the coronary blood flow increased, and the myocardial oxygen consumption remained constant. Their pooled data indicated that the normal heart became more efficient during the 10 per cent oxygen stress. In interpreting the ballistocardiographic changes with anoxia, the above-mentioned physiologic effects must be kept in mind.

An attempt was made to eliminate the respiratory influence on the BCG by having the subjects hold their breath at mid-position for the 5 to 10 seconds during each time interval in which data were recorded. However, with anoxia the increased depth of respiration which precedes each held mid-position breath is bound to induce a greater venous inflow to the heart. If the increased venous returned is not handled entirely by increased heart rate, then there may be some stretching of the myocardial fibers. According to Starling's law there would be an increased force of cardiac contraction. Thus, indirectly the respiratory factor may be playing a minor role in increasing the force of cardiac ejection seen with anoxia.

Each subject studied showed a reactive tachycardia, yet, as was pointed out in the results, the percentage increase in the tachycardia showed no correlation with the percentage increase in the cotangent HI angle. Furthermore, from preliminary experiments being carried out in this laboratory, induced tachycardia with atropine does not make the HI angle more acute. Therefore, it is unlikely that the increased rate of cardiac ejection with anoxia is produced by the increased heart rate.

A major point of consideration is the effect of diminished peripheral resistance on the HI wave during hypoxia. In the low-resistance states of severe anemia, thyrotoxicosis, and aortic insufficiency an acute HI angle generally is seen. Darby[6] has pointed out that if the diastolic pressure level falls and the cardiac contractile force, as measured by a strain gauge, remains constant, then less energy is needed to overcome peripheral resistance, and more cardiac energy is available to accelerate the bolus of ejected blood. It is quite likely that diminished peripheral resistance is one of the factors responsible for the increased HI amplitude seen with hypoxia.

Hypoxia, in addition to diminishing the peripheral resistance, may act on the heart directly, or indirectly via a neuroendocrine mechanism, to increase the myocardial contractile force. If this does occur, it would produce an increased cardiac ejection force and would in part account for, and explain, the increased HI amplitude. Also, with increased cardiac contractile force, aortic impact would occur earlier, and it would secondarily shorten the time duration of the HI wave. It appears, therefore, that the central cardiac contractile force and the level of peripheral resistance are the major factors determining the shape of the HI wave.

Interpretation of Experimental Results.—The physiologic effects of hypoxia on the cardiovascular system give some understanding into the origin of the HI wave and help explain some of the qualitative changes in HI slope seen with the 10 per cent oxygen test. As recorded in the results, there was considerable variability in the degree of the response to hypoxia. Subject 6 showed the most exaggerated response throughout the hypoxic period. This subject may well have been more hypoxic than the other 5 subjects. Without simultaneous oximetry it is difficult to say whether this is or is not the case. The effective level of the peripheral resistance may have been lowered more in this individual by the hypoxia than in the other 5 subjects. On the other hand, a marked increase in the cardiac contractile force may have been the factor primarily responsible for

the extreme response observed. It is interesting that this subject was in his early thirties and was somewhat older than the other subjects. Thus, the age factor may have played a role through an over-all exaggerated cardiovascular response to stress.

It should be pointed out that Subjects 3 and 6, both of whom were overweight, showed a significantly slow return to the basal state during the recovery period. This delayed recovery suggests that some type of physiologic debt persisted. It may reflect an exaggerated contractile force even after the hypoxia, and thus it may indicate undue cardiac strain. However, the results may reflect only that obese subjects drop their peripheral resistance for a longer length of time after an hypoxic stress than do individuals of normal weight.

Subject 5 is interesting in that at rest the HI angle of his BCG closely approximated the HI slope seen in the records of the other 5 subjects after 19-20 minutes of 10 per cent oxygen. His basal level of peripheral resistance may have been considerably less than that of the other 5 subjects, or he may have had an augmented contractile force at rest. If the latter were the case, the heart of this individual during a resting state may well be under constant stress. Subject 5 may reflect a unique category of patients heretofore unrecognized by standard methods of cardiac evaluation. It should be noted that Subject 2 had a significantly lower rate of cardiac ejection during the recovery period than during the resting state. In this individual the cardiovascular response to 10 per cent oxygen was certainly shorter lived than that in Subjects 3 and 6. It is interesting that Subject 1 did not show a cardiovascular response until the last 2 minutes of the anoxia, and even then it was relatively minimal as compared with that of the other 5 subjects. To interpret the cardiovascular significance of the results in these subjects, arterial oxygen saturation and peripheral resistance values would have to be known.

Errors.—Probably the largest error inherent in the determination of the HI slope is the assumption that the HI wave is uniformly a straight line. This is not the case, and thus the HI line that is drawn is only an approximation of the true HI slope. The HI wave is occasionally interrupted in its mid-slope by a small upstroke wave. The slope of the HI wave may be curvilinearly concave or convex, or both. Also, the H and/or I points may be reduplicated. Despite these considerations, the angle of the HI line is quite consistent when consecutive complexes are measured on the ballistocardiographic trace according to the procedure set down. Also, repetitive measurements of the HI angle on a given HI complex vary by less than one degree, and thus the HI-angle measurement has inherent reproducibility.

As was pointed out in the results, the indirect calculation of the H-I time interval is more accurate than direct observation. The reason for this fact is somewhat involved. In the direct estimation of the HI amplitude or H-I time duration, two independent observations are made in the location of the H and I points. The total error may be as great as the sum of the errors involved in each independent observation. As pointed out in the methods section, the H and I points can be located to the nearest 0.5 mm. If the average HI amplitude is 10 mm., then the maximal error would be 10 per cent. If the average H-I time

duration measures out to 3 mm., then the error involved may be as great as 33 per cent. In the calculation of the H-I time interval from the HI amplitude and the tangent to the HI angle, the following formula is used: H-I time duration = HI amplitude × tangent HI angle. The error of alignment when the HI line is drawn is known from psychophysical principles to be negligibly small.[21] The error involved in obtaining the HI amplitude would be no greater than about 10 per cent, as explained above. However, this amplitude error when figured into the calculation for the total H-I time interval would be reduced by a factor equal to the tangent HI angle, i.e., by a factor generally of about one third, assuming the average HI angle to be about 15°. That is, the total error involved in the indirect calculation of the H-I time interval is reduced considerably from that of the direct measurement. Actually, the indirect error approaches a level of 10 per cent, which is about one third the error of the direct measurement.

The HI Slope as Related to Cardiology.—Since the slope of the HI wave is determined in part by the rate of cardiac contractility, then the HI angle should reveal some information about cardiac load or stress. Recently in our laboratory, two 20-year-old overtly healthy males were seen whose records showed a very vertical HI wave (HI angle of less than 5°), and, in addition, their electrocardiograms had inverted T waves in the lateral precordial leads. It seems reasonable that an acute ejection pattern with a narrow HI angle reflects a rapid development of cardiac contractile force. This sudden stress upon the myocardium may be of sufficient magnitude to effect the ventricular gradient and invert the T wave in the electrocardiogram of these individuals.

At the present time most ballistocardiograms have been taken on resting subjects. Since the heart is a pump, a much greater insight into its dynamic status would be revealed under stress. Certainly the 10 per cent oxygen in the present experiment brought out a wide variation of cardiovascular responses, even in so-called normal subjects. This type of response is to be compared with the stress electrocardiogram which attempts only to separate normal from abnormal persons. Penneys,[20] using the Starr high-frequency ballistocardiographic bed, reported striking changes in the ballistocardiograms of coronary suspects during four attacks of anoxia-induced angina, sometimes before the onset of pain or the appearance of changes in the ECG. It is evident, therefore, that the resting BCG leaves much to be desired. Stress ballistocardiography may give a more accurate differentiation among the various cardiac states.

SUMMARY

The slope of the initial systolic deflection (HI wave) on the acceleratory ballistocardiogram reflects the rate at which the cardiac ejection force is generated. In 6 normal subjects studied, the resting value for the rate of cardiac ejection was quite variable from one individual to another. A standard hypoxic stress (10 per cent oxygen for 20 minutes) significantly increased the rate at which the cardiac ejection force was generated in all 6 subjects. The slope of the HI deflection is discussed in terms of its relation to, and reflection of, the cardiac contractile force and the peripheral resistance.

ADDENDUM

Since this article was written, Dr. Isaac Starr has reported a necropsy ballistocardiographic study on the estimation of the initial cardiac forces.[22] He concluded that from the slope of the HI segment, one can estimate the initial cardiac forces which cause the initial acceleration of the ejected blood, with an accuracy equal to that of many good clinical methods.

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The Use of Intravenous Hyaluronidase Following Narrowing of the Left Circumflex Coronary Artery in Dogs

George Lumb, M.D., M.R.C.P., and John B. Cook, III***
Memphis, Tenn.

INTRODUCTION

A recent report[1] has suggested that the intravenous injection of hyaluronidase may have some effect in modifying the development of the injury to the cardiac fibers during the first hours that follow an acute coronary occlusion. It has been suggested that the effect may result from diminution of edema, the presence of which might impair the opening up of collateral circulation and injure the myocardial fibers by compression.

We have been studying the formation of infarcts and other effects which follow narrowing of the left circumflex coronary artery in dogs without producing complete occlusion of the lumen.[2,3] It seemed important therefore to compare the results in our control series with any differences which might occur if hyaluronidase were injected intravenously following the partial arterial occlusion.

MATERIAL AND METHODS

Unselected mongrel dogs of both sexes, weighing between 22 and 35 pounds, were used for these experiments. Basal anesthesia was maintained with intravenous 6.5 per cent sodium pentobarbital (1 ml. per 5 pounds of dog body weight). A thoracic incision was made through the fourth left intercostal space. The pericardium was opened, the left atrium retracted with a spring clip, and a 2-O silk suture passed around the proximal part of the artery with an aneurysm needle. A blunted hypodermic needle, bent to an angle of 135°, was then laid alongside the vessel, and the ligature securely tied onto the needle, which was then removed. In this way the lumen of the artery was narrowed to that of the diameter of the needle used. Care was taken to perform the last part of the procedure as quickly as possible so that the artery would remain completely occluded for a minimum period. It is estimated that blood flow along the vessel was stopped completely for only a matter of 10 to 20 seconds at the maximum. In previous experiments,[2] 18, 20, and 22 gauge needles have been used, and the results obtained suggest that the size of infarct and the death rate increase with increasing narrowing of the lumen.

From The Institute of Pathology, University of Tennessee, Memphis, Tenn.
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*Professor of Pathology, Institute of Pathology, University of Tennessee. Present address: Pathologist and Director of Laboratories, James Walker Memorial Hospital, Wilmington, N. C.
**Graduate Student, Institute of Pathology, University of Tennessee.

It was decided to use the 20 gauge needle size for the comparative experiments because this procedure produces a well-defined infarct and approximately 50 per cent mortality in the control group.

Standard Lead II electrocardiographic observations were made in all of the experiments. Oscillographic records were observed throughout the surgical proceedings, and tracings were made at suitable intervals before, during, and after the operation until the animal died or was sacrificed.

RESULTS

Experiment I.—The operation with narrowing alone of the left circumflex artery was performed twelve times and 6 animals died (50 per cent). Two died within 20 minutes, 1 died at 9 hours, and 3 died at 18 hours. No gross evidence of infarction was seen in this group, but the 3 animals which survived 18 hours showed microscopic evidence of early acute myocardial infarction of the posterior wall and interventricular septum, with infiltration with neutrophil leukocytes. The 6 animals which survived showed gross evidence of infarction. In 3 cases the lateral and posterior walls of the left ventricle were involved, whereas in the other 3, only the lateral wall was affected. Microscopically, all 6 dogs showed typical healing infarcts, and the 3 larger ones showed patchy involvement of the interventricular septum.

TABLE I

DOG NUMBER	DOSE—6 HOURLY (UNITS)	INFUSION	SURVIVAL
190.	30,000	−	Sacrificed 7 days
191.	30,000	−	Died 20 min.
192.	100,000	−	Sacrificed 7 days
193.	100,000	−	Sacrificed 7 days
194.	100,000	−	Died 4 hr.
197.	200,000	−	Died 18 hr.
198.	200,000	−	Died 40 hr.
199.	200,000	−	Sacrificed 7 days
201.	100,000	−	Died 24 hr.
202.	100,000	−	Died 18 hr.
203.	100,000	+	Died 15 hr.
204.	100,000	+	Died 18 hr.
205.	100,000	+	Sacrificed 8 days
206.	100,000	+	Sacrificed 7 days
207.	100,000	+	Sacrificed 10 days
211.	100,000	−	Died 12 hr.
215.	100,000	−	Sacrificed 7 days
217.	100,000	−	Sacrificed 7 days

18 dogs: 9 survived, 9 died.

In all cases, electrocardiographic changes occurred immediately after the application of the ligature (Fig. 1, *A* and *B*). They showed abnormalities of the S-T segment which varied in severity from one animal to another. No correlation could be found between severity of appearance and prognosis. Varying degrees

of progression were seen, with a tendency to a sudden increase in severity between 4 and 7 hours following ligation (Fig. 1,*E*). In those animals which survived, the maximum period of ECG abnormality was between 18 and 24 hours. Subsequently, slow improvement occurred until the time of sacrifice.

Four animals in this group showed striking improvement in the ECG pattern, with a return to a nearly normal appearance within the first hour (Fig. 1,*C*). From this point onward, however, progression of abnormality was noticed which was essentially similar to that of the other cases in this group.

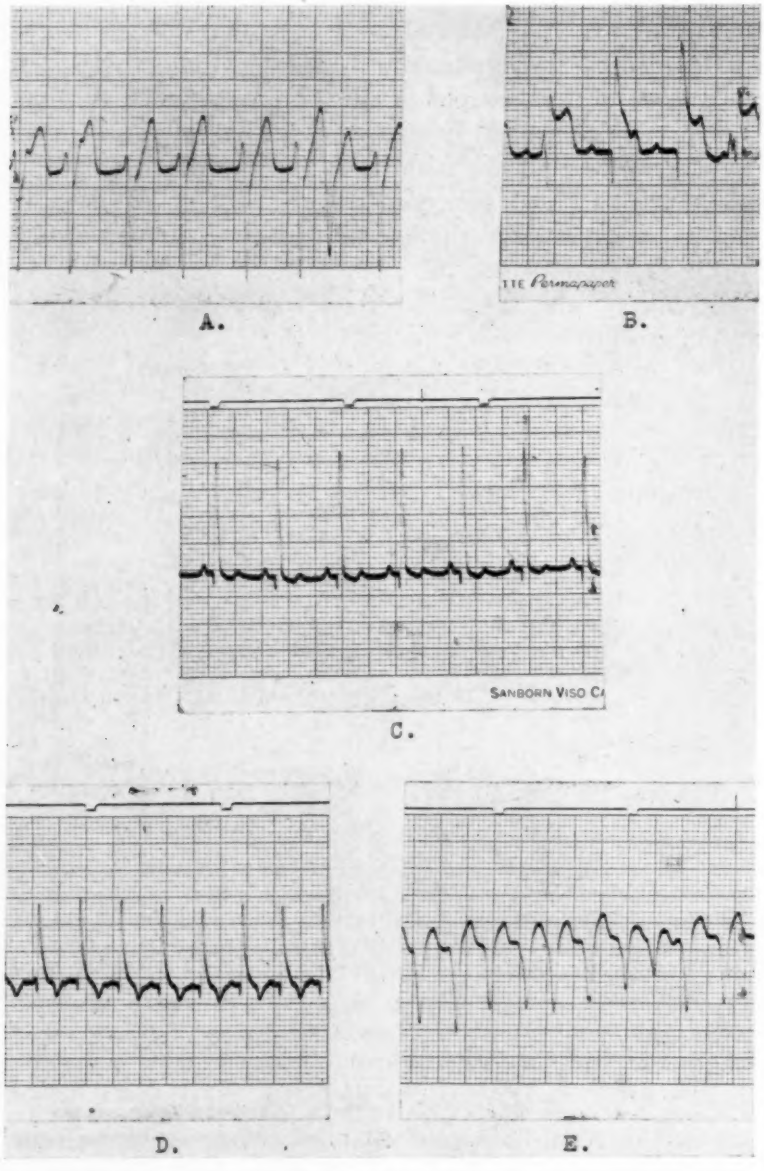

Fig. 1.—Lead II of the electrocardiogram. *A* and *B*, Abnormal pattern immediately after ligation. *C*, Return to a nearly normal pattern 30 minutes after ligation. *D*, Appearance at 2 to 4 hours after ligation with moderate S-T segment abnormality. *E*, Severe damage pattern at 8 hours after ligation.

Experiment II.—In 18 dogs the operation of narrowing the left circumflex artery was performed as before, but hyaluronidase was injected in various doses, as shown in Table I.* Intravenous injection was used in all cases. An injection was given at the time of ligation in 14 dogs. It was delayed for 5 hours in 3 dogs, and for 30 minutes in 1 dog. Doses of 30,000 units were used in 2 dogs, 200,000 units in 4 dogs, and 100,000 units in 13 dogs. Following the initial dose, subsequent similar doses were given at 6-hourly intervals for 24 hours if the dogs survived. In 5 animals a constant, slow intravenous infusion of hyaluronidase was given during the first 8 hours after ligation. The infusion was adjusted so that 100,000 units were given during a 4-hour period.

There was no correlation between the method of dosage and the survival rate (see Table I). Nine of the 18 dogs died in less than 48 hours, and 9 survived to be sacrificed at 7 to 10 days following operation. In those dogs which lived longer than 24 hours, infarcts were visible which were similar in distribution to those seen in Experiment I. Microscopic appearances showed typical healing infarcts with involvement of the interventricular septum in 5 cases.

There were no significant differences in the electrocardiographic appearances in this group from those seen in Experiment I, with the possible exception of the 5 cases in which constant infusion was given during the first 8 hours. In the 13 cases without infusion, improvement in the ECG pattern within the first hour to a nearly normal appearance was noted in 6 animals (Fig. 1,*C*). Subsequently, progression occurred in the same manner as in the control group in Experiment I. The 5 dogs which received an infusion of hyaluronidase showed less severe ECG changes during the first 4 to 5 hours (Fig. 1,*D*), but their subsequent progression showed no difference from that of the other dogs. It must also be noted that 2 of these 5 animals died at 15 and 18 hours.

DISCUSSION

There are no differences between the results of Experiments I and II which suggest that hyaluronidase plays any part in preventing or modifying the formation of an infarct or in improving the prognosis in the dog. The size and distribution of areas of infarcted muscle, and the survival rates were identical in the two series of experiments. The tendency for the ECG pattern to show a return toward a nearly normal appearance during the hour following ligation of the vessel was seen in an approximately similar number of cases in both groups. The only feature which might be interpreted as suggesting a beneficial effect from the administration of hyaluronidase was seen in the 5 cases in which continuous infusion of the drug was given during the first 8 hours. Although no improvement in survival rate or in the production of infarcts was noted, the ECG changes seemed to be less severe during the first 4 to 6 hours.

If further experiments are designed to investigate any possible effects of hyaluronidase, it seems that the maintenance of a high concentration of the drug in the blood stream during the period following narrowing of the lumen would be advisable.

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*Hyaluronidase was used in the form of Wydase, which was supplied by Wyeth Laboratories, Philadelphia, Pa.

SUMMARY

Partial occlusion of the origin of the left circumflex coronary artery has been performed in 12 dogs.

Intravenous injections of hyaluronidase have been given to 18 dogs in which partial occlusion of the left circumflex coronary artery was performed.

A comparison of the results in the two groups is made.

No evidence was obtained which indicates that hyaluronidase influences the production of infarcts or the survival rate in dogs under the conditions of these experiments.

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On the Interpretation of Cancellation Experiments. II

Richard McFee, Ph.D., Syracuse, N. Y.

The concept of local and remote leads, of "intrinsic" and "extrinsic" deflections in electrocardiographic recordings, has been questioned in recent years by a number of investigators,* chiefly on the basis of experimental work with cancellation leads. In their studies these investigators have found that the voltages obtained from several leads attached to the human body could be balanced, one against the other, so as to produce a fairly high degree of cancellation during the QRS interval. This is a result which can be explained easily if one assumes that the electromotive forces during the QRS interval effectively originate from a small region of the heart muscle, and it has been natural to use this explanation to account for the results of the experiments. But this explanation, if correct, means that the electromotive forces accompanying the excitation of the heart can be completely described in terms of a single time-varying dipole located in this small region, and this, in turn, implies that chest leads, bipolar leads, esophageal leads, etc., can furnish no more information about excitation than can be extracted from a good vectorcardiographic lead system. This conclusion is at variance with conventional electrocardiographic theory, and many have questioned whether the ability to attain good cancellation does, in fact, imply that the heart's electromotive force originates from a small region.*

In a previous paper[1] a direct test of this question was made. Using a mathematical model, independent time-varying dipoles were placed at a variety of separated points in a volume conductor, and an attempt was then made to balance, one against the other, voltages induced in four different leads. Reasonably good cancellation was obtained in all of the seven cases studied. Furthermore, it was also found that the voltages induced in local electrodes near the electromotive forces could not be predicted with accuracy from knowledge of three components of the resultant of all the forces. Thus it was clear that good cancellation in volume conductors does not require that the electromotive forces be located at or near a point, nor does it imply that local leads are superfluous.

From the Department of Electrical Engineering, Syracuse University, Syracuse, N. Y.

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*For references see Reference 1 of this article.

The degree of cancellation that can be achieved with fairly widely separated, independently fluctuating electromotive forces is at first surprising. A theory which accounts for this cancellation, based on an approach originally proposed by Brody and his associates, is outlined in this article.

The theory accounts for the cancellation in the following manner. The cancellation leads have sufficient flexibility to permit adjustment to give triple zero crossings of the cancelled output. Because the high-frequency content of electrocardiograms is limited, this means that the cancelled residue will have a low amplitude. The amplitude is reduced still further by the weakness of the lead field in the heart region which generally (although not always) occurs automatically when the lead is adjusted to give a triple zero crossing.

In order to simplify the discussion, it will be restricted to the cancellation lead proposed by Becking and Burger (see Fig. 1). The arguments can be extended with some qualifications to more complex cancellations leads, such as those proposed by Schmitt and others.

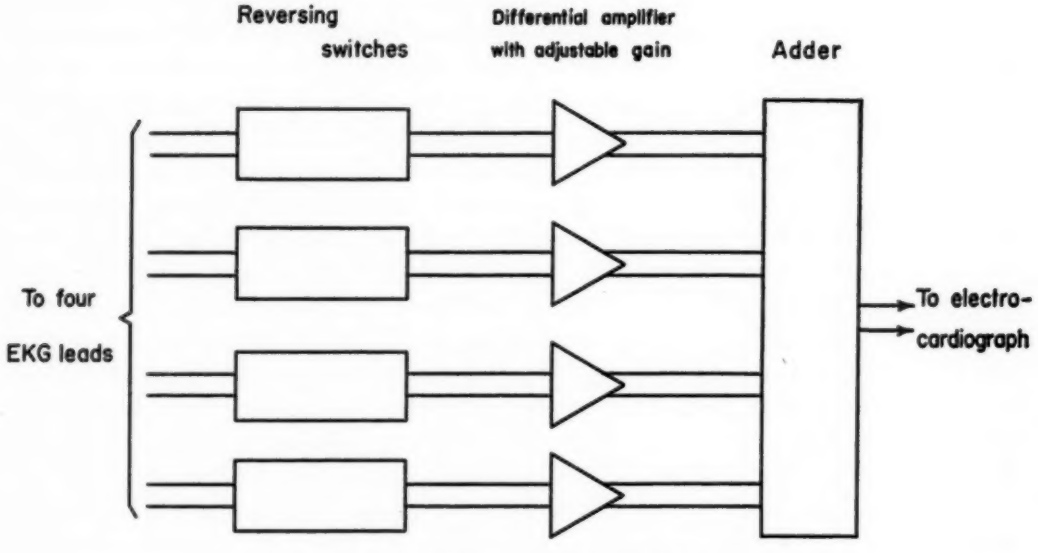


Fig. 1.—The Becking-Burger cancellation lead.

THE WEAK LEAD-FIELD EFFECT

A distinguishing feature of the Becking-Burger cancellation lead is its three controls which may be adjusted to vary the amplitudes and the polarities of three lead voltages, relative to the fourth voltage to which they are added. The object of the adjustment is to find a setting for all three controls that will give a small residual for the sum of the four voltages. Burger[2] has shown that the controls can always be set to make the lead insensitive to the effects of dipoles located at any one point in the body, and from this it follows that the output of the cancellation lead can be made zero if the heart's electromotive forces are, indeed, located at a point. Some further consequences of this fact will now be discussed.

Burger actually showed that the lead vector of the cancellation lead can be made zero with regard to dipoles located at any specified point. Since this lead vector is equal to the strength of the current field in the body which results when a current of one ampere is introduced into the lead* (the "lead field"), it means, therefore, that the lead field at that point is zero, i.e., that there is a "point of stagnation" or "null" of the lead field where the dipole is located. Near the null the lead field is exceedingly feeble; consequently, the lead vectors are very small, and the lead relatively insensitive to dipoles located in that region. Hence, if the cancellation lead is made insensitive to the effect of a dipole near the middle of the heart, the lead will be relatively insensitive to the effects of electromotive forces anywhere in the heart, and its output voltage consequently will be low.

The reduction of the strength of the lead field in the vicinity of a null depends mainly upon the proximity of the lead electrodes involved. A quantitative estimate of this reduction is found in Appendix I, in which it is shown that the reduction factor is roughly D/2q, where D is the diameter of the heart, and q is the distance from the lead electrodes to the heart center. Thus, if the electrodes are about two diameters from the center of the heart, the output voltage of the Becking-Burger cancellation arrangement can be reduced to about one fourth of the average voltages in the four constituent leads.

THE EFFECT OF MULTIPLE ZERO CROSSINGS

The controls of the cancellation lead need not be adjusted so that the lead field in the heart region is weak. They can, if desired, be set so that the output of the cancellation lead crosses through zero three times during the QRS complex. That this is always possible is shown in Appendix II. An insight into the effects of such an adjustment can be achieved by breaking the QRS complex down into its low- and high-frequency components. These frequency components are shown in Fig. 2. Mathematical theory establishes that such a breakdown is always possible. It is not difficult to verify this quantitatively by combining the components in various ways so as to produce typical QRS complexes, as is shown in Fig. 3. These artificial complexes are very similar to the complexes recorded from human subjects.

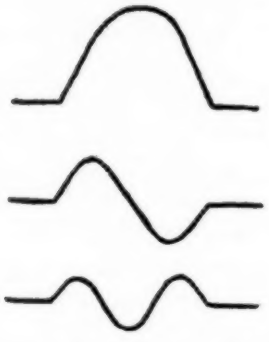
In fact, it is evident from Fig. 2 that the first three frequency components are able to account for the greatest part of electrocardiographic voltages, and that only a relatively small amount of the higher frequency components need be used to achieve a perfect match. If a perfect duplication were possible with the first three components, and if the output of the cancellation lead were adjusted so that there were three zero crossings during the QRS interval, the lead output would have to be zero, since three zero crossings imply a four-spike deflection, yet no combinations of the one, two, and three-spike components shown in Fig. 2 can give a four-spike wave. With QRS complexes which contain a small

*Of course, the Becking-Burger cancellation lead ordinarily contains amplifiers which would prevent the flow of current backward through them to the subject, but there always exists an equivalent network of resistors which will produce the same output, except for a constant factor, and it is understood that the current is applied to this equivalent network.

percentage of the higher frequency components, adjustment of the lead to give a triple zero crossing will leave a small multiphasic residue, and this is the type of output typically found in most cancellation experiments.

The lack of high frequencies is due largely to the character of the heart's electromotive forces themselves, but it is emphasized to some degree by the limited frequency response of some electrocardiographs, which tends to round off corners and soften sharp spikes.

Fig. 2.



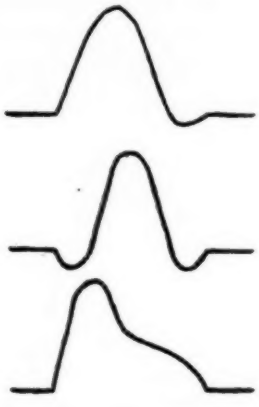


Fig. 3.

Fig. 2.—Basic frequency components of the "QRS" complexes of electrocardiograms. These are the first three terms of a Fourier "sine" series. The terms are defined to be zero outside the QRS interval. Such a series can be made to approximate any continuous function, with arbitrarily small error within the interval. Outside the interval the value of the series will be zero.

Fig. 3.—Combinations of basic frequency components which simulate typical electrocardiograms.

The cancellation that results from the limited high-frequency content of recorded electrocardiographic voltages can be estimated by obtaining electrocardiograms from four different persons, plotting them on the same time scale, and cancelling them one against the other. Because the subjects are different, there can be no question of cancellation due to the weak lead field. The procedure involved here, although simple in principle, is quite tedious. It has been carried out in a total of five cases, using the voltages shown in Fig. 2 of the preceding paper.[1] The ratio of the peak deflection of the cancelled residue to the mean peak deflection of the four complexes added was found to have an average of 1/3. It is evident from this result that the limited high-frequency content of electrocardiographic voltages can account for a considerable amount of cancellation.

COMBINATION OF EFFECTS

Suppose that the controls of a cancellation lead have been adjusted so that the voltage crosses through zero three times during the QRS complex, with a consequent reduction in the output voltage. Will the strength of the lead field in the heart region also be reduced, thus producing a further reduction in the lead voltage?

It is an important feature of cancellation leads that this will usually happen. The theoretical reasons are developed in Appendix III. It is not difficult to see qualitatively why it should be so. If the lead output is to be zero three times

during the QRS complex, it is necessary that the field of the lead be almost perpendicular to the resultant of the heart's electromotive forces at those instants. In other words, the components of the lead field in the three directions taken on by the heart vector at the three instants involved must be small. If these directions are substantially different, it is necessary that the field itself be small, for if it were not, its projection along one of the axes would be substantial. A similar argument can be applied to a moving ship. If it is known to have only a small velocity component in a northerly direction, and a small component also in a southwesterly direction, then it follows that the ship itself must be almost stationary, because it cannot go in any direction at good speed without having substantial velocity components in the directions mentioned.

Thus it is seen that cancellation due to weak lead-field effects and to multiple zero crossing generally occur simultaneously, yielding a combined cancellation ratio given by the approximate equation

$$R \simeq \left(\frac{D}{2q}\right)\left(\frac{1}{3}\right) \tag{1}$$

In this equation, R is the ratio of the peak voltage of the cancelled residue to the average of the peak voltages of the four constituent leads of the Becking-Burger cancellation system at the point of addition. D is the effective diameter of the heart, and q is the distance of the closest electrode to the heart center. If the electromotive forces of the heart were located in a sphere 1 cm. in diameter, as has been stated in the literature, giving the heart an effective diameter of 1 cm., and if the closest lead electrode were 15 cm. away, then the predicted cancellation ratio is $1/(2 \times 3 \times 15)$ or 1/60. Thus, an average peak voltage of one millivolt in the four waves being added would call for a cancelled residue with a peak less than 20 microvolts. This is far better cancellation than is attained in practice.

It should be kept in mind that the foregoing equation gives a rough approximation of a statistical average, and that considerable variation above and below the value predicted is to be expected.

EXCEPTIONAL CASES

The discussion thus far has indicated the order of magnitude of the cancellation to be expected statistically, if the electromotive forces are more or less uniformly distributed throughout the heart, and if the voltages vary at a rate typical of most electrocardiograms. However, it is possible to get much better or worse cancellation for reasons which will now be outlined briefly.

An important exception occurs when the electromotive forces of the heart continually point in directions perpendicular to some axis, i.e., their directions lie in a plane. If the fields of the four leads lie more or less in the same plane, than the cancellation can turn out to be quite a bit better than predicted by the equation. But if the fields of the leads are more or less perpendicular to the plane, it is possible to obtain triple zero crossings without at the same time having a weak lead field, and the maximum reduction achievable will be of the order of D/2q or 1/3, whichever is smaller.

If the cancellation ratio is defined as the ratio of the peak of the cancelled residue to the voltage of the "reference" lead, as cancelled by a linear combination of voltages of the other three leads, then a considerable variation of cancellation ratio is possible simply by selection of the reference lead. For example, suppose that best cancellation is achieved with a peak voltage of 2, 1, 0.7, and 0.4 millivolts, respectively, in the four leads added, and suppose also that the cancelled residue has a peak of 0.1 millivolts. If the reference lead now is the one with the peak of 2 millivolts, the cancellation ratio is 0.05, but if the reference lead is the one with a peak of 0.4 millivolts, the cancellation ratio will be 0.25. Of course, use of the average peak voltage in determining the ratio eliminates this difficulty.

The cancellation will tend to be good if all the lead electrodes are clustered in one area of the body surface relatively distant from the heart, or if the voltages produced by the heart tend to be of a simple monophasic type. Cancellations will be better in a lead with more degrees of freedom, such as Frank's lead, in which five parameters can be varied to achieve optimum balance, than it will be with the Becking-Burger lead or Schmitt's lead, in which only three parameters can be varied.

Cancellation will tend to be poor when all lead electrodes are in the immediate vicinity of the heart, or when all the lead voltages are multiphasic in character, such as those recorded from "transitional regions" of the body.

CONCLUSION

It was shown in the preceding paper that cancellation leads can usually be adjusted so that their output voltages are low, even when the electromotive forces are distributed throughout the volume conductor and vary independently from one point to the next. In this article a theory of this cancellation is discussed, which accounts for it in terms of two factors: (a) the weakness of the lead field in the heart region, and (b) the multiple zero crossings of the cancelled residue.

It is evident from both test and theory that the existence of cancellation does not imply that the heart's electromotive forces are effectively located in a small portion of its muscle, or that proximity potentials do not exist.

APPENDIX I

A null in a lead field is a point at which the field strength is zero. A dipole located at such a point will produce no effect on the lead; conversely, if there is a point at which a dipole may be located without influencing the lead, regardless of its orientation, then the lead field will have a null at that point.

Lead fields will always be weak in the neighborhood of To see why this is so, express the three components J_x, J_y, J_z of the lead field J in terms of expansions of the type

$$\begin{aligned} J_x &= J_{xo} + d_x x + f_x y + g_x z + \text{Terms in } x^2, y^2, z^2, xy, x^3, \text{ etc.} \\ J_y &= J_{yo} + d_y x + f_y y + g_y z + \text{Terms in } x^2, y^2, z^2, xy, x^3, \text{ etc.} \\ J_z &= J_{zo} + d_z x + f_z y + g_z z + \text{Terms in } x^2, y^2, z^2, xy, x^3, \text{ etc.} \end{aligned} \qquad (2)$$

where x, y, and z are the displacement of the point from some reference point, at which the field $\vec{J}$ has the three components J_{xo}, J_{yo}, J_{zo}. The coefficients d, f, and g are related by divergence con-

ditions which need not concern us here. If the reference point is a null of the field, and J_{xo}, J_{yo}, and J_{zo} consequently are zero, it is evident from equation (2) that the field itself must be small when x, y, and z are small, i.e., in the vicinity of the null.

The strength of the field in the vicinity of the null depends on the closeness of the lead electrode and the size of the region. A quantitative estimate of the average strength of the null field in the heart region as a function of electrode distance has been obtained for the idealized* case illustrated in Fig. 4. Here the heart is represented as a sphere, a part of an infinite homogeneous conductor. The cancellation lead includes one lead taken between an exploring electrode near the heart and a second remote electrode at the opposite side of the heart. It also includes a second

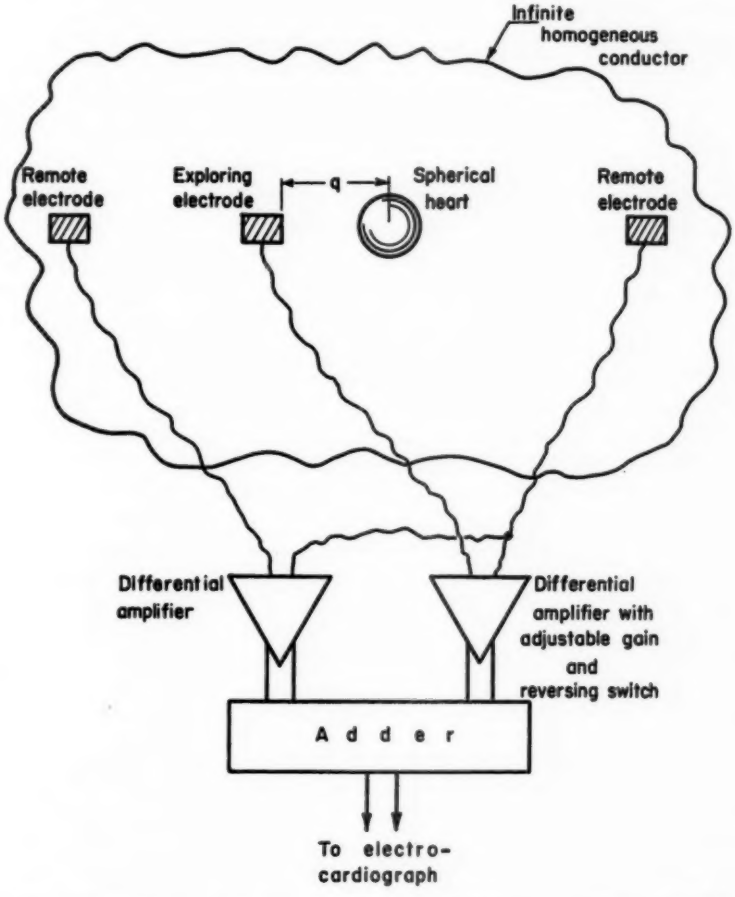


Fig. 4.—The elementary cancellation lead used to determine the magnitude of the weak lead-field effect.

lead taken between the aforesaid remote electrode and another equally remote electrode on the opposite side of the heart. The combining factors for these two leads are adjusted so that the cancellation lead field is then the same as the "error field of a unipolar lead," which was studied quantitatively in a previous article.[3] In the appendix of that article it was found that in the heart the ratio of the average strength of this error field to the average strength of the field of the remote

*The situation shown in Fig. 4 can be considered to represent a Becking-Burger cancellation arrangement in which three of the constituent leads have electrodes which are very remote, and the fourth lead has one electrode located remotely and a second locally. The three remote leads will produce in the heart region a uniform field, which can also be produced by a single lead such as that shown in Fig. 4. When the arrangement has been adjusted for cancellation, the axes of the leads will coincide as in Fig. 4.

electrode pair is given approximately by the expression $\frac{D}{2q}$, where q is the distance from the exploring electrode to the center of the heart, and D is the diameter of the heart.

According to this equation, when the exploring electrode is at the surface of the heart, i.e., $\frac{D}{2q}$ is one, the cancellation lead field will have the same average magnitude as the lead field of the remote lead. In other words, at this distance from the heart, there will not be a reduction in the cancellation lead voltage because of the relative weakness of the lead field. But if the exploring electrode is two diameters from the center of the heart, then the cancellation lead field is only one fourth of the average magnitude of the field of the remote lead.

APPENDIX II

It is necessary to show that the Becking-Burger cancellation lead can be adjusted to give an output with a triple zero crossing. Thus, it is required to find coefficients a, b, and c such that

$$\begin{aligned} a\,V_1(t_1) + b\,V_2(t_1) + c\,V_3(t_1) &= V_4(t_1) \\ a\,V_1(t_2) + b\,V_2(t_2) + c\,V_3(t_2) &= V_4(t_2) \\ a\,V_1(t_3) + b\,V_2(t_3) + c\,V_3(t_3) &= V_4(t_3) \end{aligned} \tag{3}$$

where $V_1(t)$, $V_2(t)$, $V_3(t)$, and $V_4(t)$ are the voltages in the leads as a function of time, and t_1, t_2, and t_3 are three different instants in the QRS interval. As long as the leads are different, there will always be a solution of equation (3) for a, b, and c, and therefore the Burger-Becking cancellation lead may be adjusted to have at least three zero crossings of its output. One can show that in most cases the Schmitt lead also may be adjusted so that it has triple zero crossings. The proof, however, is quite complicated, there are many special cases, and it is therefore omitted here.

The maximum number of zero crossings that can be attained is determined by the number of degrees of freedom of the lead. With the Burger-Becking lead there are three knobs to twist, thus three degrees of freedom, and hence a triple zero crossing is possible. With the Schmitt lead there is one knob to twist and two ways in which the "search" electrode can be moved, up and down, or left to right, so that in it, too, a triple zero crossing is possible. With the Frank cancellation lead the ability to move a potentiometer tap, as well as two electrodes in two directions each, gives a total of five degrees of freedom. This means that Frank's lead can in some cases be adjusted to give five zero crossings. With all of these leads there are special cases in which the maximum possible number of zero crossings cannot be obtained.

APPENDIX III

The objective of this appendix is to show that the lead field will be small in the heart region when the cancellation lead has been adjusted so that it has multiple zero crossings. The analysis will be given for the simple case in which the field of the heart originates from a dipole, the magnitude, orientation, and location of which vary as the beat progresses. (Note that this is not a "fixed location dipole.") Extension to the case in which there are n dipoles, n arbitrarily large, is easily made, and results in the same conclusions.

Express the lead voltage at the three instants t_1, t_2, and t_3 in terms of the dot product of the dipoles $\vec{D}_1$, $\vec{D}_2$, and $\vec{D}_3$ at these instants and the lead fields $\vec{J}_1$, $\vec{J}_2$, and $\vec{J}_3$ in which it is located. If the lead voltages at the three instants have been made zero, the following equations apply:

$$\begin{aligned} \vec{D}_1 \cdot \vec{J}_1 &= 0 \\ \vec{D}_2 \cdot \vec{J}_2 &= 0 \\ \vec{D}_3 \cdot \vec{J}_3 &= 0 \end{aligned} \tag{4}$$

The lead field vectors $\vec{J}_2$ and $\vec{J}_3$ can be expressed in terms of $\vec{J}_1$ as follows:

$$\vec{J}_2 = \vec{J}_1 + \vec{\Delta}_2 \qquad \vec{J}_3 = \vec{J}_1 + \vec{\Delta}_3 \tag{5}$$

Here $\vec{\Delta}_2$ and $\vec{\Delta}_3$ represent the change of the lead field in going from the point at which the dipole

is located at t_1 to the points at which it is located at the other two instants. As has been shown previously, if the electrodes of the cancellation lead are not located in the immediate vicinity of the heart, these changes will be small compared to the field of the reference lead. Rewriting the equations of (4) in terms $\vec{J}_1$ and $\vec{\Delta}_2$ and $\vec{\Delta}_3$ gives

$$\vec{D}_1 \cdot \vec{J}_1 = 0 \tag{6a}$$

$$\vec{D}_2 \cdot \vec{J}_1 = -\vec{D}_2 \cdot \vec{\Delta}_2 \tag{6b}$$

$$\vec{D}_3 \cdot \vec{J}_1 = -\vec{D}_3 \cdot \vec{\Delta}_3 \tag{6c}$$

Assuming that $\vec{D}_1$ is not zero, the first of these equations implies either that $\vec{D}_1$ and $\vec{J}_1$ are at right angles, or that $\vec{J}_1$ is zero. In either case the component of $\vec{J}_1$ in the direction of $\vec{D}_1$ is zero. Equations (6b) and (6c) show that the components of $\vec{J}_1$ in the directions of $\vec{D}_2$ and $\vec{D}_3$ are equal to the components of $\vec{\Delta}_2$ and $\vec{\Delta}_3$ in those directions, respectively. Since the changes in the lead field are small, the components of these changes will be even smaller. This means that the components of $\vec{J}_1$ in these two directions will be quite small.

If the components of $\vec{J}_1$ in three different directions are small or zero, $\vec{J}_1$ itself will generally* have a small magnitude. An exactly similar development shows that the lead fields $\vec{J}_2$ and $\vec{J}_3$ will also be small. Since the changes in the lead field between these and other points in the heart are small, it follows that the lead field will be weak throughout the entire heart region.

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*An exception is the special case in which $\vec{D}_1$, $\vec{D}_2$, and $\vec{D}_3$ all point in directions lying in a plane.

A Technique for Simultaneous Pressure Determination in the Left and Right Sides of the Heart

J. R. Derrick, M.D., G. W. N. Eggers, Jr., M.D., J. J. Leonard, M.D., and H. W. Paley, M.D., Galveston, Tex.

A simple technique for the simultaneous determination of the pressure in the right and the left sides of the heart would be valuable in cardiac diagnosis and physiologic studies. Pressures of the left atrium have often been determined by the transbronchial approach[1-3] and the posterior percutaneous approach.[4,5] Recently, Ross,[6,7] introducing a curved needle into the femoral vein through a catheter and puncturing the interatrial septum, has taken pressure readings from both atria. Securing pressures from needle exploration of the heart chambers at surgery suggested to us a simple means of obtaining simultaneous pressures from the right and the left sides of the heart. Our objective was to pass a long needle safely through the chest wall into the right atrium, then direct the needle through the interatrial septum into the left atrium.

TECHNIQUE

Review of a series of angiocardiograms had revealed that the right atrium normally extends superiorly to the second right intercostal space, inferiorly and anteriorly to the sixth intercostal space, and slightly medial to and almost parallel with the right sternal border. The interatrial septum constitutes the posteromedial wall of the right atrium. With the patient in the supine position, a needle,* consisting of two 18 or 20 gauge needles welded together with the orifices 2.5 cm. apart (Fig. 1), was inserted slightly medial to the right sternal border at the level of the fourth or fifth right intercostal space. It was then progressively reinserted, being moved laterally by minute amounts until it eventually cleared the sternal edge. Then, kept constantly in contact with the sternal edge in order to avoid puncture of the internal mammary vessels (Fig. 2), the needle was directed posteriorly and medially toward the center of the vertebral column, the only resistance encountered being that of the pericardium and the interatrial septum. In patients with an intact interatrial septum, the location of each needle aperture was ascertained by the color of a small quantity of blood withdrawn in a syringe. Simultaneous measurement of pressures was then performed utilizing Statham strain gauges and a multichannel recorder.

Seven patients were studied by this technique. All procedures were performed in the operating room with the patient under general anesthesia with the electrocardiogram monitored. A thoracotomy was then performed on 6 patients, and at this time the site of the needle puncture

From the Departments of Surgery, Anesthesiology, and Internal Medicine, University of Texas Medical Branch, Galveston, Tex.

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*Needle made by Pemco Inc., Cleveland, Ohio.

was assessed and the appearance of blood in the pericardial space noted. After completion of the procedure, and surgery, if any, a chest roentgenogram was made in order to discover a possible pneumothorax, since the course of the special needle might, in some instances, penetrate the medial aspect of the right lung. On one patient, we performed a simultaneous left ventricular puncture, employing the method described by Brock.[8] On one patient who underwent the study no operative procedure was performed. He was carefully observed for 2 hours in the operating room and 2 hours in the recovery room, for evidence of cardiac tamponade.

Fig. 1.—Double-lumen needle with offset orifices for simultaneous measurement of pressures on both sides of the interatrial septum.

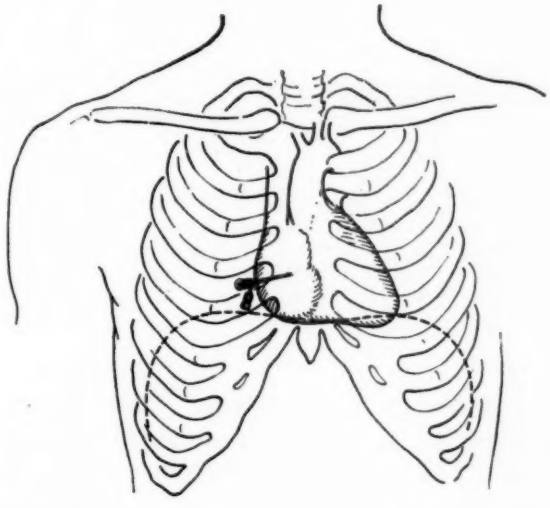

Fig. 2.—Illustration of the correct placement of the needle to pierce the right atrium and interatrial septum.

RESULTS

In every case the needle was correctly placed on the initial attempt. Manipulation of the needle was unnecessary. Arrhythmias were either absent or brief, limited to occasional premature atrial contractions as the right atrium was pierced.

Pressures obtained from a patient with mitral stenosis are illustrated in Fig. 3. After the needle was inserted, both needle orifices were noted to be in the left atrium. The long tracing (*A*) illustrates the withdrawal of the needle until both atrial pressures were observed. The shorter tracings (*B*, *C*) illustrate the pressures before and after the needle was positioned.

Only one complication occurred; 50 c.c. of blood were found in the pericardial sac of a patient who underwent thoracotomy. We believe that the leakage was caused by the left ventricular puncture which had been performed on this patient.

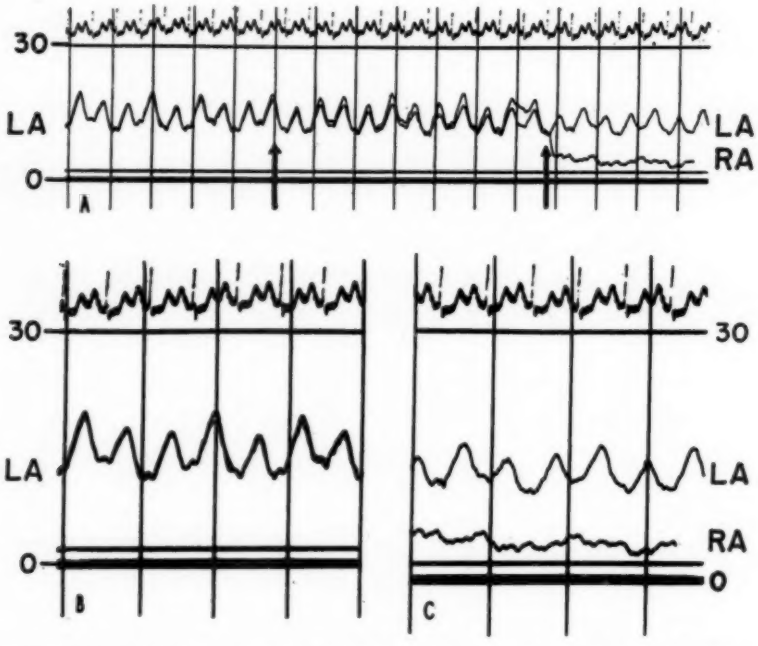

Fig. 3.—Simultaneous tracings of right and left atrial pressure in a patient with mitral stenosis. *A*, Both needle orifices were in the left atrium at the left portion of the tracing; the section of the tracing between the arrows was made as the needle was withdrawn. Right and left atrial pressures are shown on the right portion of the tracing. *B*, Close-up of tracing *A* before the needle was withdrawn. *C*, Close-up of tracing *A* after needle was withdrawn. *LA:* Left atrium. *RA:* Right atrium. ECG recorded in Lead II.

DISCUSSION

Broad experience with the transbronchial approach seemed to make it the most dependable method for left atrial studies at the present time. If additional work confirms the safety of these procedures reported here, however, it may prove valuable in situations requiring simultaneous left and right heart studies. Placement of small plastic catheters into either or both sides of the heart is now possible, and injection of indicators or radiopaque substances would be be very informative. Investigations of the pulmonary circulation utilizing this technique are now in progress also. It may later prove practical to perform the procedure with only a local anesthesia. The patient's supine position would not interfere with the performance of other studies.

The site of puncture in the technique presented is particularly advantageous because of the low pressure in the right atrium. If the left atrial pressure is elevated, as in mitral stenosis, and leakage occurs, it would empty into the right atrium rather than into the pericardial space. Ross has reported that no left-to-right shunt resulted from puncture of the interatrial septum even in the presence of an elevated left atrial pressure.[7] Careful attention to the irrigation of the tubing and needle before inserting the needle into the left atrium seems ad-

visable so as to prevent an air embolus. A much broader experience with this technique seems desirable before the authors can recommend its use.

SUMMARY

A new technique for the simultaneous determination of pressures in the left and right heart is described. A double-lumen needle was inserted through the anterior chest wall, right atrium, and interatrial septum into the left atrium. Offset orifices made possible the simultaneous measurement of pressures on both sides of the interatrial septum. Advantages and suggested uses of this technique are discussed.

No complications attributable to this procedure have been observed, and the authors feel that it may be valuable clinically as soon as its safety has been confirmed by additional work.

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Case Reports

Idiopathic Cardiac Hypertrophy of Long Duration

Mosche Gueron, M.D., Cincinnati, Ohio*

Cardiac hypertrophy of obscure origin is the dominant feature of a group of cases presenting distinctive clinical and pathologic syndromes. The clinical diagnosis of idiopathic cardiomegaly is a challenge to the physician in spite of several reviews of the subject.[1-4] The diagnosis is not easily entertained beyond the age of 50, and always remains elusive and unexplained both to the clinician and the pathologist because of the rarity of the cases, and also because of the divergent views on the possible etiological factors causing many of the syndromes similar to the one reported here, e.g., subendocardial fibroelastosis,[8-11] idiopathic myocarditis,[15-17] endomyocardial fibrosis,[18-20] nutritional heart diseases,[13,14] myocardial collagenosis,[12] restrictive endocarditis,[5] fibroblastic endocarditis with eosinophilia.[6,7] The subject of this report is a patient who died in congestive failure, 22 years after a routine chest x-ray film revealed unexplained left ventricular enlargement, and in whom the pathologic examination did not reveal the usual etiological factors for myocardial hypertrophy.

CASE REPORT

A 51-year-old clerk was admitted to The Jewish Hospital on June 2, 1958, for swelling of both ankles. He was apparently well up to 3 weeks prior to admission, when he noticed some shortness of breath on exertion and swollen legs. After he was treated with chlorothiazide, the swelling disappeared, but returned on May 28, 1958. The right leg was painful, tender, and apparently more swollen than the left. Previous history was unremarkable, but he had been told that he had a large heart, and in 1937, a routine pre-employment x-ray film had been interpreted as showing enlargement of the left ventricle (Fig. 1). He had been very active and never limited in exercise. On examination he was a well-developed, well-nourished, white man, acutely ill, without respiratory distress. The blood pressure was 110/70 mm. Hg, and the pulse rate was 80. There was no neck vein distention or pulsations, and the thyroid was not enlarged. Moist râles were heard posteriorly at both lung bases. The heart was enlarged to the left anterior axillary line, with a diffuse impulse in the sixth intercostal space, and definite right and left ventricular heaves

From the Cardiovascular Pulmonary Unit, Department of Medicine, The Jewish Hospital and Medical Center, Cincinnati, Ohio.

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*Present address: Cardiac Laboratory, Department of Medicine, Cincinnati General Hospital, University of Cincinnati Medical College, Cincinnati, Ohio.

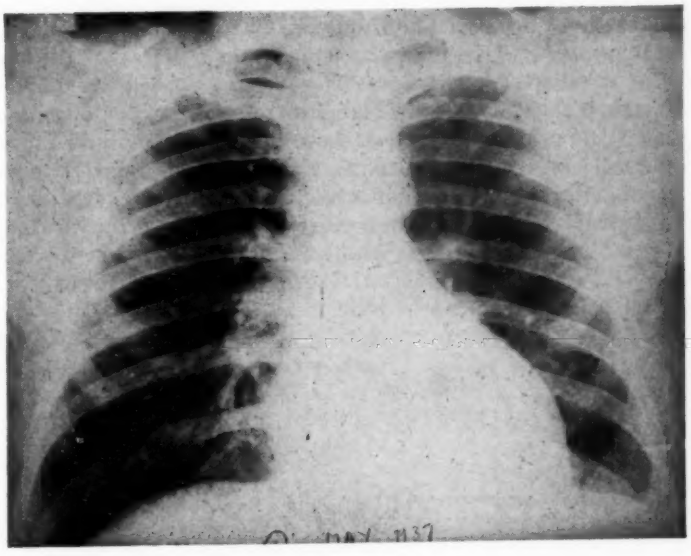

Fig. 1.

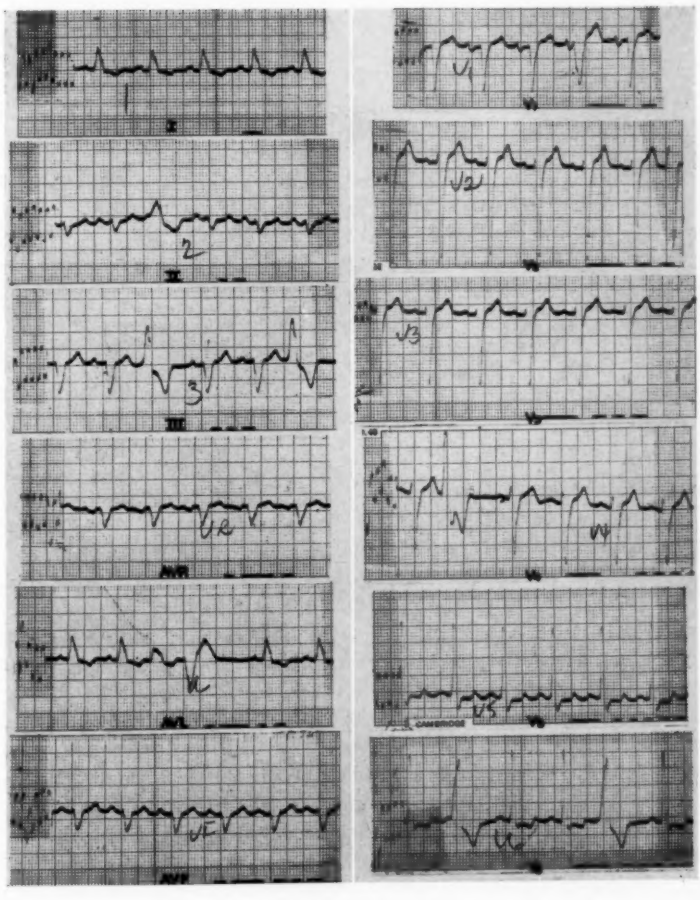

Fig. 2.

were felt. No murmurs were heard. Heart sounds were of good quality, and aortic and pulmonic closures were equal. The liver was enlarged 6 to 8 cm. The spleen was not palpable. Peripheral pulses were normal. Four-plus ankle edema was noted. The right calf was tender and hot; Homan's sign was positive. Red blood cell count was 4,000,000/c.mm., hemoglobin 12.9 Gm., white blood cell count 10,100/c.mm. with a normal differential. Serologic tests for syphilis were negative. Plasma protein was 6.3 Gm. per cent. Urinalysis showed 5 mg. per cent protein; no sediment was reported. The electrocardiogram recorded at the time of this admission is shown in Fig. 2. Fluoroscopy revealed no abnormal pulsations or valvular calcification. An x-ray film of the chest showed marked generalized cardiac enlargement, transverse diameter 21 cm., with congestive changes in the lungs and a small amount of fluid at both bases. The patient was treated for congestive failure and phlebitis, with marked improvement. The edema disappeared, tenderness of the right calf subsided, and after 9 days he was discharged.

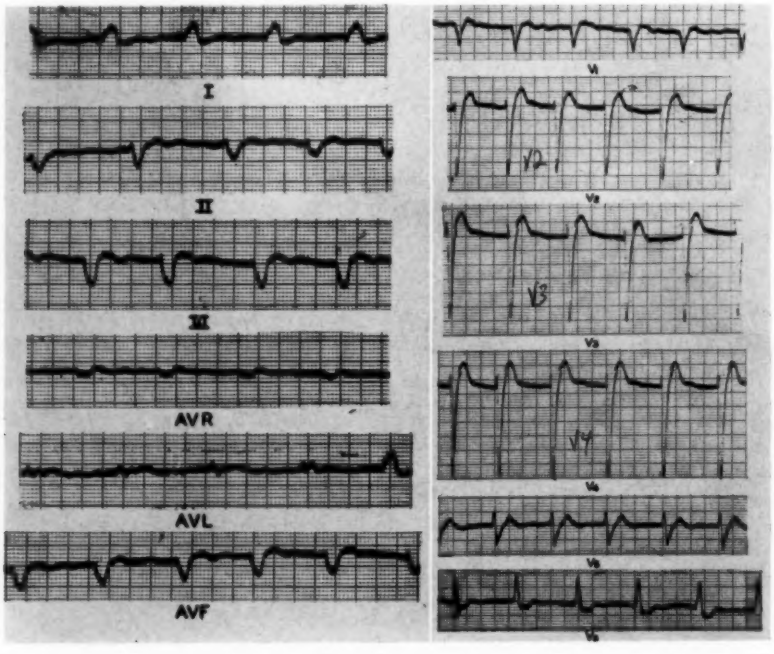

Fig. 3.

He remained well, active, and untreated until 3 weeks before his second admission, on March 2, 1959. This time he complained of shortness of breath on exertion, severe edema of the lower part of the body, and respiratory distress which was relieved by the use of three pillows. He denied any chest pain, or recent febrile illness. The findings of the physical examination were slightly different from those of the previous admission. The neck veins were distended and pulsating, with prominent V waves. A Grade 2 regurgitation systolic murmur, suggesting relative tricuspid insufficiency, was present at the left sternal border in the fifth intercostal space, increasing in intensity with inspiration. At the apex there was a Grade 1 holosystolic blowing murmur, interpreted as being due to relative mitral insufficiency, which did not change with the respiration. The liver was enlarged and showed pulsations with systole. Optic fundi were normal. Venous pressure on admission was 26 cm. of water; arm-to-tongue circulation time was 53 seconds. Laboratory studies were normal, except that plasma chlorides were 86 mEq./L., sodium was 135 mEq./L., potassium was 4.2 mEq./L. Urinalysis showed occasional white blood cells, with 40 to 50 red blood cells per high-power field, and protein of 50 to 60 mg. per cent. The electrocardiogram recorded at the time of this admission is shown in Fig. 3. An x-ray film revealed some haziness of the left lower lobe, with small pleural effusion, due most probably to pulmonary infarction (Fig. 4).

The patient responded very poorly to treatment. Anticoagulants were not given properly. The prothrombin time did not go below 50 per cent. He became drowsy, more edematous, and lapsed into a semicomatose state, with severe respiratory distress and prominent cyanosis. He expired on the fourteenth day of this admission. The clinical diagnosis was congestive failure of unknown origin with pulmonary and renal emboli.

Necropsy Findings.—The chief necropsy findings were in the heart, which weighed 800 grams, was greatly enlarged, moderately firm, and somewhat globular in shape (Fig. 5). The visceral pericardium was generally smooth, except for a white circumscribed area of thickening, approximately 3 cm. in greatest diameter, located on the lateral wall of the right ventricle. A number of punctate hemorrhages were present in the subepicardial fat, particularly at the apex of the heart, but also scattered over the left ventricle, both atria, and the pulmonary conus. All four chambers were dilated, and the right (8 mm. thick) and left (17 mm. thick) ventricles were thicker than usual despite the dilatation. The endocardium was irregularly thickened and opaque, particularly over both surfaces of the intraventricular septum, toward the apex of both ventricles, and over the trabeculae carneae of the left ventricle. In the right and left auricles were fairly large mural thrombi, firmly attached to the wall. Small areas of firmly attached blood clot were also present in the interstices of the trabeculae of the left ventricle. The endocardium of the valve leaflets was smooth, thick, and pliable, and the chordae tendineae were thin, not shortened, and not fused. The tricuspid valve was 14.5 cm. in circumference, whereas the rest of the valve rings were within normal limits of size. Multiple cross sections of the three major branches of the coronary arteries revealed only minute calcified plaques, not encroaching in the lumina. The rest of the arterial walls was impressively thin and pliable. Multiple sections through the myocardium did not reveal any large scars, recent necrosis, or hemorrhage.

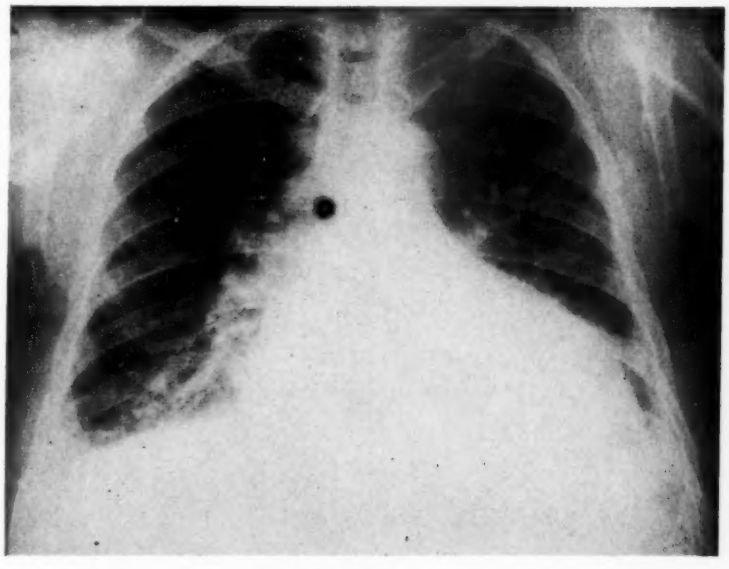

Fig. 4.

Microscopic Findings.—Microscopic examinations of the sections of the atria confirmed the presence of organizing mural thrombi of varying age. The interstitial tissue was congested, edematous, and increased in amount. In the centers of some of the trabeculae the muscle was necrotic. The atrial muscle fibers were hypertrophied, and these areas were infiltrated by acute inflammatory cells and hemorrhage. The atrial endocardium and epicardium were thickened, and the latter was focally infiltrated by small numbers of mononuclear cells.

The myocardium of the ventricles was also remarkable for the greatly increased width of the muscle fibers and the markedly enlarged nuclei of irregular or rectangular shape (Fig. 6).

Although numerous fibers were not thickened, the majority were moderately to markedly hypertrophied. The endocardium was unevenly thickened by collagenous and elastic fibers. The subendocardial muscle fibers were often partly replaced by dense collagenous scar tissue extending only a short distance in the myocardium. Dense collagenous tissue was also present around small intramural vessels, partly replacing adjacent muscle fibers in some places. Dense collagenous tissue was also increased in the base of the A-V valves. Vacuolization was present in some areas, but was not prominent. The perinuclear pigment was not unduly increased in amount. The interstitial tissue, in addition to the widespread focal collagenous thickening mentioned, was

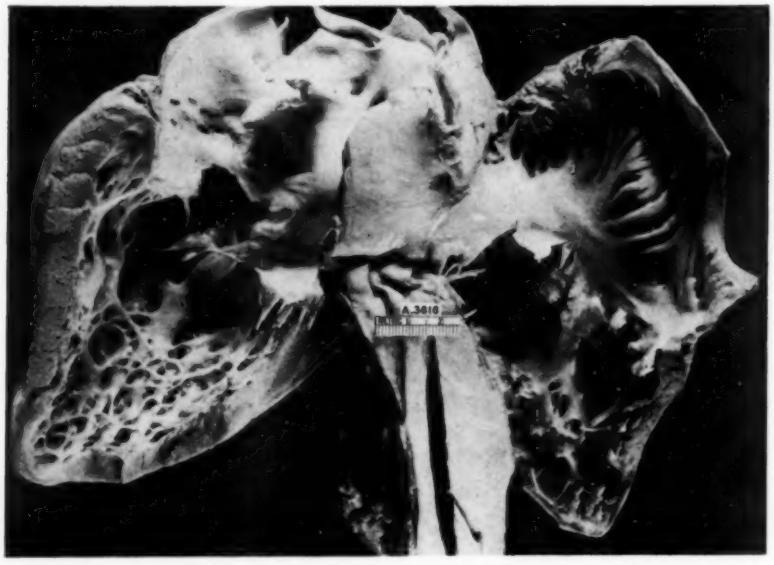

Fig. 5.

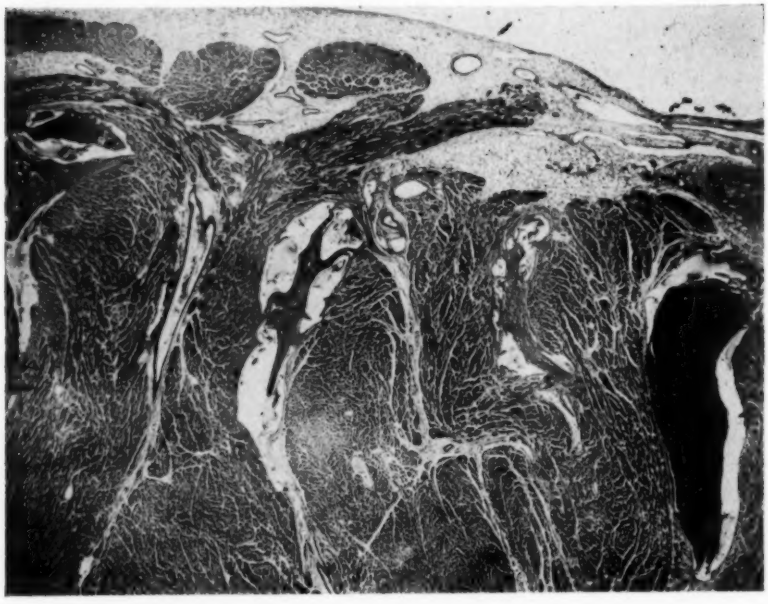

Fig. 6.

congested, loose, and abundant, and unevenly infiltrated by a light sprinkling of mononuclear cells. No focus of acute necrosis was found in any of the sections other than that from the atrium. The inflammatory infiltration varied in amount and type of cells, with lymphocytes predominating.

Petechial hemorrhages were found in some sections of the myocardium, as well as the grossly described focal hemorrhages in the subepicardial fat of the apex. Special staining was limited to crystal violet stain for amyloid, which was negative. The other histologic findings were not remarkable, except for kidney infarction and pulmonary artery embolus.

COMMENTS

There appeared to be little doubt that the reason for death was resistant heart failure complicated by recurrent pulmonary and kidney emboli and severe electrolyte disturbances. Some of the clinical features seen in our patient, such as prominent right heart failure, high venous pressure, tricuspid insufficiency, and left ventricular hypertrophy, implied Bernheim's syndrome, but this possibility was dismissed. We also discarded as possibilities constrictive pericarditis and "stiff heart"[5] ("constrictive endocarditis"), as suggested by Littman in a recent discussion,[21] because these could not explain the train of events in this case. The only possibility which was difficult to eliminate was coronary heart disease, especially in view of the patient's age and the presence of left bundle branch block with atrial fibrillation. But this diagnosis would be unlikely, especially with the negative past history and the abnormal x-ray picture recorded 22 years ago. As far as etiology was concerned, it was clear that none of the common causes of hypertrophy were present. We excluded amyloidosis and hemochromatosis as etiological factors of the long-standing cardiac enlargement. Also, there was no evidence that the clinical picture was the result of healed beriberi or other nutritional cardiopathies.

In reviewing the literature on the diseases of the myocardium and the endocardium, one frequently encounters descriptions of the heart showing varying degrees of endocardial thickening, myocardial hypertrophy, and fibrosis under a variety of names and different conditions. Various authors have attempted to implicate a number of etiological and pathogenetic mechanisms in cases of this type. The possible relationship of our case to idiopathic myocarditis occurring as a primary entity[16,17] or associated with infectious diseases,[25] virus infection,[15] was considered as a remote possibility, although myocarditis has no distinctive nor uniform pathologic pattern, and all gradations in the histologic picture have been described: from severe muscle necorsis and cellular infiltration to slight fibrosis. The contention that the pathologic changes in this case were due to myocarditis in the past seemed unlikely after 22 years of an uneventful clinical course and the absence of a history of any acute process. It was also not possible to label our case as endocardial fibrosis, a syndrome complex presenting different histologic findings, as described by Gray,[28] who suggested that this may be an "ill-defined category of collagen disease," and who postulated that the clinical and pathologic resemblance of the cases occurring in Africa[13,14,18-20] to those found elsewhere does not imply that the cause is necessarily identical. Apparently, the reports cited have dealt only with cases in Africans and have described pathologic changes different from those reported in the present paper.

Recently, in a symposium, Davis,[19] emphasizing the characteristic histologic features, protested the confusion of endomyocardial fibrosis[18,20] with other similar disorders such as fibroelastosis, nutritional heart diseases, or Löffler's endocarditis.[6,7] Shafer, in the same symposium, suggested that myocardial fibrosis might be a modified form of rheumatic heart disease. Becker,[12] reporting cardiovascular collagenosis, produced evidence which suggests that the condition is due to disturbances of the connective tissues of the heart and should be classified with the other collagen diseases. Although such findings might be a feature common to a number of different cardiopathies, it is difficult to accept these suggestions in the absence of the classic lesions of collagen diseases as described by Klemperer.[29] Also, there is nothing to suggest that our case is the result of, or belongs to the group of, cardiac collagenosis, nor that it is some forme fruste of collagen disease. Fibroelastosis[8] is a rare finding in adults,[9-11] seldom involving the right ventricle, and affecting the valves in approximately one half of the cases. Usually, the myocardium is not extremely hypertrophied; the coronary vessels are sometimes involved. Our case presented different histologic changes, and it would be difficult to accept, at the present stage of studies, that idiopathic cardiac hypertrophy is some form of fibroelastosis. Weisman[30] uses the absence of myocardial changes as one of the criteria of true fibroelastosis. Fibroelastosis lacks specificity and is seen in a number of other cardiopathies as severe coronary sclerosis with small infarctions.[9]

From the clinical and pathologic points of view, the case reported here is very similar to those described by Elster and associates[1]; but none of their cases had had a long-standing cardiac enlargement. Elster also did not believe that there is a common denominator in adult fibroelastosis and idiopathic cardiac hypertrophy, nor in any of the other aforementioned clinicopathologic syndromes. He did not clarify the etiology of idiopathic cardiomegaly in his extensive pathologic studies, and several authors did not consider this entity as a unit per se.[22-24] Other investigators ascribed to hypoxia and intracardiac stasis following congestive failure the subendocardial necrosis and Thebesian vein thrombosis,[26] and, subsequently, foci of mural and subendocardial fibrosis. To still others, the hypertrophy per se might result in fibrosis.[27]

It is clear that the types of heart diseases with fibrosis of the endocardium, myocardium with hypertrophy, present considerably difficult problems. Are they different diseases, different etiological causes with more or less similar pathologic pictures, or is this a single disease process? Do known factors play any role in the causation? These are difficult questions to answer at the present moment.

SUMMARY

A case of long-standing cardiac hypertrophy and subsequent myocardial failure of unknown origin has been described. Common etiological factors have been excluded. The clinical course was short, when congestive failure developed, progressive, and complicated by emboli. At necropsy, the outstanding finding was marked myocardial hypertrophy. There were no abnormalities in the coronary vascular tree, pericardium, aorta, or cardiac valves. No additional clue as to the etiology of the hypertrophy was discovered.

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Unusual Vascular Ring Formed by the Anomalous Left Pulmonary Artery, With Tracheal Compression

Gen Niwayama, M.D., Buffalo, N. Y.

Compression of the trachea in infants is most frequently caused by enlarged mediastinal lymph nodes or a retroesophageal abscess. Such marked swelling of the lymph nodes has been observed in lymphoblastomas and during recent caseation necrosis of primary tuberculosis of the lung leading to very massive, caseated, complex changes in the upper tracheobronchial and paratracheal lymph nodes. Less commonly the trachea may be compressed by congenital vascular rings and other anomalous structures in the mediastinum. In some cases the dilated pouch of the cephalic segment of a congenitally atretic esophagus impinges upon the trachea from behind, thus compressing it. Vascular ring, as a clinical concept, denotes those anomalies of the aortic arch system which cause symptoms of tracheal and esophageal compression. Unlike other malformations of this system, including coarctation of the aorta and patent ductus arteriosus, there are no cardiac signs or symptoms associated with vascular ring. In 1926, Arkin[1] gave the first roentgenologic account of this condition verified by postmortem examination. Since Gross[2] reported successful surgical repair of this vascular anomaly in 1945, clinical diagnosis of vascular ring is recognized as an indication for surgical intervention. Recently, at postmortem examination, an unusual type of vascular ring formation with tracheal compression was found, in which anomalous origin and course of the left pulmonary artery caused the tracheal compression.

CASE REPORT

The patient, a white female infant, was first admitted to the hospital at the age of 2½ months. She had had difficulty in breathing since birth, as stated by the parents.

Family History.—Father, 31 years old; mother, 30 years old. One sister, aged 13, in good health.

Neonatal History.—Nine months' duration of pregnancy. Length of labor, 4 hours. Vertex presentation. Spontaneous delivery. Birth weight, 5 pounds and 13½ ounces. Mother in good health all the time. No disease during pregnancy.

From the Departments of Pathology, Children's Hospital and the Medical School, University of Buffalo, Buffalo, N. Y.

Received for publication Aug. 10, 1959.

Present Illness.—The baby was born in the hospital and breathed well at birth. During the first few days the mother noticed that the breathing of the baby became noisy. The baby also had diarrhea, which lasted for about 2 months. She had been given skim milk in order to clear up the condition. For a few weeks prior to admission, cream had been added to the diet, but the diarrhea recurred. Two days prior to admission the mother noticed, while bathing the child, that the chest was retracting with each respiration. Shortly thereafter the child vomited and aspirated; this happened three to four times. The infant was in acute respiratory distress, with retractions and gargling sounds. No blueness was noted. One day prior to admission, chest x-ray examination* with barium swallow established the diagnosis of "aberrant vessel" obstructing the trachea.

Fig. 1.—Anterior view of the heart and great vessels. *A*: Aorta. *LPA*: Left pulmonary artery. *RPA*: Right pulmonary artery. *LCCA*: Left common carotid artery. *RCCA*: Right common carotid artery.

The patient was referred to the Children's Hospital, Buffalo, N. Y. Physical examination on admission (July 4, 1958, 1:20 P.M.) showed the following: The temperature was 100 F., the pulse was 160, and the respirations were 55. The baby was cyanotic and gasping, in acute respiratory distress, breathing with marked inspiratory retraction. There was no stridor. Nose and throat were injected. The neck was supple. No distention or palpable mass were observed in the abdomen. Oxygen was given by mask. Adrenalin (1:1000) was injected into the left arm. Bronchoscopy was attempted, but without success. Then an upper tracheotomy was performed. At a later time, tenacious bloody mucus was obtained from the trachea. The child suddenly turned cyanotic and stopped breathing. Immediate thoracotomy and heart massage were without results. The child expired at 5:45 P.M. on the same day.

Autopsy Findings.—The pertinent findings were: A well-developed, 2½-month-old white infant girl in a good state of nutrition, with slightly cyanotic lips and fingernail beds. The brain was grossly of normal appearance.

The dome of the diaphragm was at the level of the fourth rib bilaterally. The trachea was stenotic along its entire course, and its diameter was 5 mm. in the sagittal and 4 mm. in the transverse plane. The left lung consisted of a single lobe; the right lung had two lobes. Both lungs were well expanded and showed a few scattered bronchopneumonic infiltrations in every lobe.

*Examination by Dr. Hughes in St. Francis Hospital, Olean, N. Y.

The undissected heart measured 4.3 cm. in transverse and 3.7 cm. in vertical diameter. The left ventricle was 5 mm., the right ventricle, 3 mm. in thickness. The valves were regular. The circumferences of the tricuspid and mitral valves were 4 cm. and 3.1 cm., respectively. The pulmonary artery measured 1.0 cm., the ascending aorta, 1.1 cm. in diameter. The foramen ovale was compensated and presented a slit-like opening. The thoracic aorta had a normal course. The aortic arch was located anterior to the trachea, and the descending part of the aorta was on the left side, lateral to the trachea, and above the left major bronchus. The common trunk of the pulmonary artery had a normal course, with the patent ductus arteriosus connecting the thoracic

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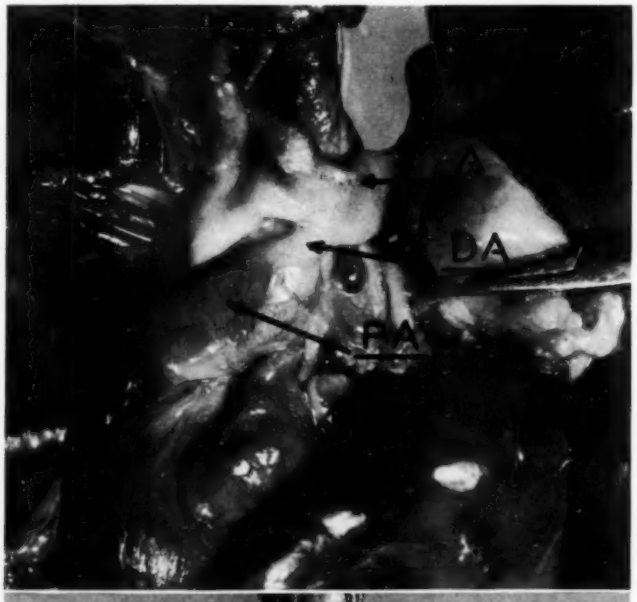

Fig. 3.

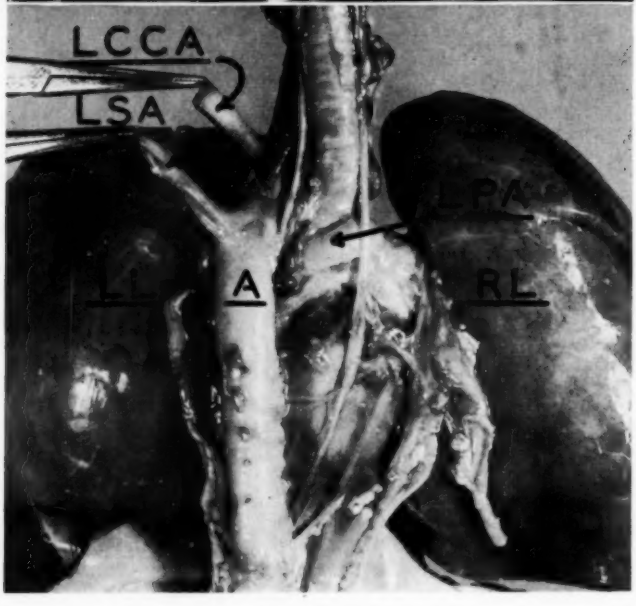

Fig. 2.—Left lateral view of the heart and great vessels. *PA*: Main trunk of the pulmonary artery. *DA*: Ductus arteriosus.

Fig. 3.—Posterior view of the heart and great vessels. *LL*: Left lung. *RL*: Right lung.

aorta. The right pulmonary artery branched off the common pulmonary trunk in normal fashion and entered the right lung with its two major branches at the hilum. The major part of the right pulmonary artery measured 0.9 cm. in diameter, the first dividing branches, 0.3 cm.

The left pulmonary artery originated from the main stem of the right pulmonary artery, immediately proximal to its division into the first-order branches, and coursed *behind the trachea, in front of the esophagus*, thus forming a vascular ring at the level of the bifurcation. The artery entered the left lung just above the left major bronchus; it measured 4 mm. in its proximal portion.

The anomalous left pulmonary artery thus circled the trachea just below the aortic arch, turning somewhat obliquely in front of the descending aorta, and dividing into its first-order branches at the hilum of the left lung.

The pulmonary veins had a normal course. There was, in addition, an anomalous course of the left renal vein, behind the abdominal aorta, but entering normally into the inferior vena cava. Except for absence of the left lobe of the thyroid, there were no other visceral anomalies present.

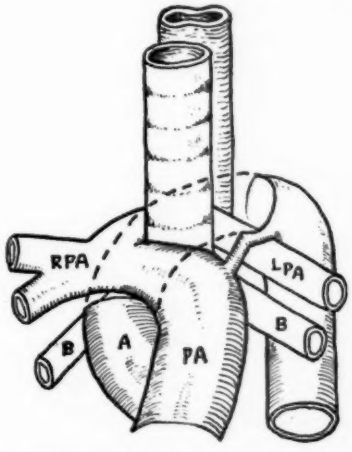

Fig. 4.—Diagram showing the relationship between the aorta and pulmonary arteries. The left pulmonary artery lies between the trachea and the esophagus. The ductus arteriosus is patent and connects the main trunk of the pulmonary artery with the thoracic aorta. *B*: Bronchus.

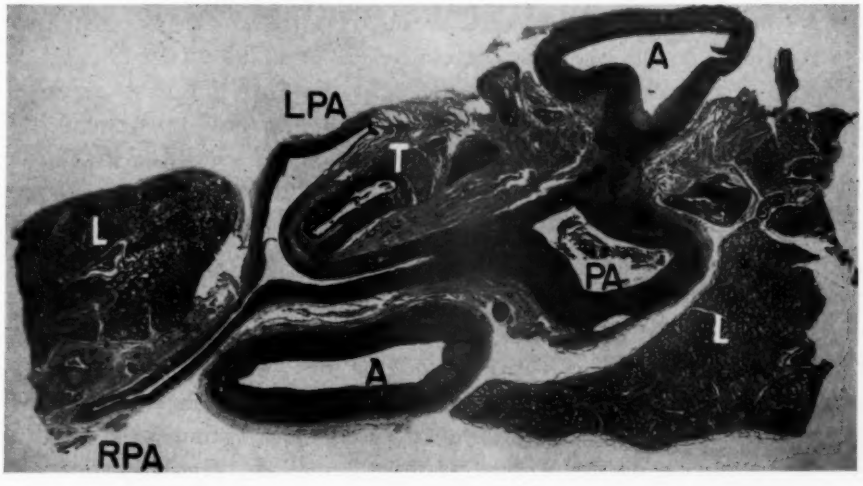

Fig. 5.—Cross section through the aorta and pulmonary arteries at the level of the ductus arteriosus. The aorta shows both ascending and descending parts. A part of the wall of the ductus arteriosus is shown between the main trunk of the pulmonary artery (*PA*) and aorta (*A*). *T*: Trachea. The esophagus is behind the left pulmonary artery (*LPA*), but is not included in this cross section.

Microscopically, there were no noticeable findings in the wall of the trachea, except for small submucosal hemorrhages. Lung sections showed small bronchopneumonic foci, edema, and intra-alveolar hemorrhages. The arterioles were not remarkable.

The major anatomic diagnoses included: (1) stenosis of the trachea; (2) abnormal origin and course of the left pulmonary artery, forming a vascular ring with compression of the trachea; (3) abnormal lobation of both lungs; (4) anomaly of the thyroid, with absence of isthmus and left lobe; (5) anomalous course of the left renal vein; (6) bronchopneumonia; (7) status following tracheotomy, thoracotomy, and heart massage.

DISCUSSION

A variety of anatomic classifications have been offered for the malformations of the aortic arches. Edwards[3] reviewed 57 reports of vascular rings and gave the following classification based on the anomalous development of the aortic arches: *Basic pattern:* Double aortic arch and double ductus arteriosus. *Subgroup A:* Left-sided ductus arteriosus and left-sided descending aorta. *Subgroup B:* Left-sided ductus arteriosus and right-sided descending aorta. *Subgroup C:* Right-sided ductus arteriosus and right-sided descending aorta. *Subgroup D:* Right-sided ductus arteriosus and left-sided descending aorta. According to Edwards, the formation of a vascular ring is the result of combined anomalies of either the aorta itself or its derivatives in association with the ductus arteriosus.

It is clear that the vascular ring encircles both the trachea and the esophagus in most cases; i.e., the anomalous vessel lies dorsal to the trachea and esophagus. In Bayford's case (1794),[4] quoted by Edwards, the vascular ring, however, is composed of the left-sided aortic arch and the descending aorta, with the right subclavian artery arising from the distal portion of the aortic arch and lying between the esophagus and trachea. Thus, the pulmonary artery does not take part in the formation of a vascular ring in the reported cases.

Recently, however, 2 interesting cases were reported in the literature. Taussig[5] has observed one case in which the dilatation of the pulmonary artery was so extreme that, with slight variation in the patient's position, the pulmonary artery so greatly constricted the trachea and bronchi as to cause attacks of cyanosis and severe dyspnea. Bronchoscopic examination showed at one time the right main bronchus, and at another time the left main bronchus, compressed to one half of its width. In this instance, Blalock attempted to alleviate the pressure symptoms by wrapping the pulmonary artery with cellophane, but the child died suddenly three hours following the operation. The autopsy revealed enormous dilatation of the pulmonary artery and its main branches, but no other abnormality of the heart.

In discussing the anomalous pulmonary vessels, Findlay and Maier,[6] in 1951, reported the case of a 4-month-old female Negro infant with chief complaints of intermittent cyanosis, dyspnea, and fever. There was confluent bronchopneumonia. The heart was enlarged. The pulmonary artery had a normal caliber. There was *one branch to the left lung, but none to the right.* One centimeter above the aortic valve a large vessel arose from the left side of the aorta. *This artery coursed behind the esophagus to enter the right lung.* The innominate and left subclavian arteries arose at their usual sites. The left common carotid artery

branched off from the innominate artery 1 cm. above its origin. The ligamentum arteriosum was normal in location. This case was the first report of an anomalous pulmonary artery encircling the trachea and esophagus, with intermittent cyanosis and dyspnea. Findlay and Maier stated that if the correct diagnosis could have been made in time, a right pneumonectomy or the division of the anomalous pulmonary artery would have benefited the infant.

In the recent literature, however, 5 almost identical cases[7-10] were reported: 2 cases in 1954, 1 in 1955, and 2 in 1956. In all 5 cases the anomalous left pulmonary artery showed similar anomalous course as seen in the case of this report. All 5 patients were males.

In 3 of these patients (Welch[7]; Wittenborg[10]), definite narrowing of the trachea at the site of the aberrant vessel was apparent. There was no significant differential aeration of the lungs, and the main interference with the mechanics of aeration appeared to be the result of compression of the trachea as seen in the case of this report. However, in one case (Wittenborg's Case 1) the narrowing was not limited to the site of the aberrant vessel, but extended well above the level that could be compressed by the vessel, and was thought to represent a congenital hypoplasia. In 2 patients (Potts[8]; Morse[9]), there was partial narrowing of the right main bronchus, with resulting obstructive emphysema on the right. According to Potts and associates, the right bronchus was "paper thin" at the point of pressure.

The onset of the symptoms occurred variously: since birth (Potts; Morse), on the fourth day (Wittenborg's Case 1), and in the second week (Wittenborg's Case 2). The characteristic symptoms were dyspnea, cyanosis, wheezing and retraction, and repeated respiratory infections.

The roentgenogram showed normal findings in 2 cases (Welch; Wittenborg's Case 2). However, moderate bilateral emphysema and narrowing of the lower trachea were described in one case (Wittenborg's Case 1), and emphysema of the right was seen in 2 cases (Potts; Morse).

The barium studies in one case (Wittenborg's Case 1) revealed a posterior indentation in the esophagus at the level of the aortic arch, running obliquely cephalad from left to right, characteristic of an aberrant right subclavian artery with a retroesophageal course.

Bronchoscopy revealed constriction of the trachea just above the carina in one case (Wittenborg's Case 1), and narrowing or compression of the right main bronchus was seen in 2 cases (Potts; Morse).

In Potts and associates' case the diagnosis of the anomalous left pulmonary artery was surgically confirmed. Right thoracotomy, section, and anterior anastomosis of the left pulmonary artery were successfully performed when the infant was 5 months old.

Associated congenital anomalies were described in 2 cases (Wittenborg); in one of them there were aberrant right subclavian artery, persistent left superior vena cava, hypoplastic left kidney, hemivertibrae, and incomplete rotation of intestine; in the other there were dextroposition of aorta, interventricular septal defect, coarctation of aorta, and possible Mongolism.

No embryologic explanation of this type of anomaly (the aberrant left pulmonary artery) was given in 3 reports (Welch; Potts; Morse). According to Wittenborg and associates, the anomaly might be explained by the mechanism of anomalous vessel formation from the primitive plexus about the esophagus and tracheal bud. As the pulmonary arches are in the process of formation by the union of sprouts from dorsal and ventral aorta (the latter actually representing the primitive pulmonary artery), an adventitious union with the intricate esophagotracheal plexus may occur. Eventually, a single channel remains, running between the trachea and esophagus.

According to Keibel and Mall,[11] in 1912, the lung bud appears early in fetal life (in the 2.5-mm. embryo) as a rounded prominence below the laryngotracheal groove. Soon this divides into two pulmonary sacs (in the 5-mm. embryo). The pulmonary vessels develop (7-mm. embryo) at the same time that the pulmonary sac is differentiating into three buds on the right and into two on the left side. Congdon,[12] in 1922, gave a detailed description of the development of the aortic arch system in the human embryo. In the second week of embryonic life, there exists a single-chambered heart. On each side of this there is an ascending or ventral aorta, aortic arch, and dorsal aorta. Toward the end of the fourth week (in the 5-mm. embryo) the ascending segments unite to form the truncus arteriosus, and the dorsal aortae combine to form a common descending aorta at a lower somatic level. Six arches soon develop on each side. These connect the anterior and posterior trunks. They do not appear at the same time, and some of them regress completely. While they are present, the anlage of the trachea and esophagus are encircled. Normally, the external carotid arteries represent the surviving parts of the ventral paired aortae. The internal carotid arteries are derived from the third arches and form the persisting cephalic portions of the original dorsal paired aortae. The segments of the dorsal aortae which lie between the third and fourth arches disappear. The proximal portion of the right ventral aorta becomes the right innominate artery. The subclavian artery on that side is derived from the fourth dorsal aorta. On the left, the fourth arch becomes the definitive aortic arch which continues as the descending aorta. The pulmonary arteries are derived from the proximal portions of the sixth arches and their branches. Only on the left does the distal half of the sixth arch persist, forming the ductus arteriosus. The division of the truncus arteriosus in the sagittal plane brings about the complete separation of the pulmonary and aortic systems.

In the case of this report the main trunk of the pulmonary artery was normally developed and well separated from the aorta as described in Findlay and Maier's case. Therefore, the anomalous development of the pulmonary artery must have taken place at about the time of the completion of the sixth arches. The development of the aortic arch system, however, is much more complex and, apparently, potentially subject to many variations. Edwards[3] presented several hypothetical types of vascular ring based on developmental consideration.

In addition, Gross and Ware,[13] in 1946, mentioned the possibility that the trachea could be compressed by the left common carotid artery arising to the right of the midline and crossing ventral to the trachea to achieve its usual position on the left side of the superior mediastinum.

In determining the diagnosis of vascular anomaly with tracheal compression all possibilities of aberrant development, not only within the aortic system but also of the pulmonary artery, should be carefully considered, including the unusual type of vascular ring reported in this paper.

SUMMARY

This is the report of stenosis of the trachea by a vascular ring formed by the anomalous course of the left pulmonary artery in a 2½-month-old infant. The anomalous left pulmonary artery originated from the distal part of the main stem of the right pulmonary artery and encircled the trachea in front of the esophagus. The role of the anomalous pulmonary artery is discussed in its relation to the embryonic development of the aortic arch system and to the other known types of vascular ring.

The author wishes to express his gratitude to Dr. Kornel L. Terplan for his supervision and guidance in preparing this paper, and to Mr. T. Llyle Keith and Mrs. Renee Monagle for their technical assistance.

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Clinical-Pathologic Conference

Jacob S. Golden, M.D., Albert I. Rubenstone, M.D., Bertram Levin, M.D., and Alfred Pick, M.D., Chicago, Ill.

CLINICAL ABSTRACT

First Admission.—This patient, an 84-year-old Caucasian male, was first admitted to Michael Reese Hospital on Sept. 13, 1951, with a 2-week history of urgency and inability to urinate. He had been catheterized several times at home, but each time that the catheter was removed, an inability to urinate became manifest. For some 6 months prior to that time he had noticed narrowing and weakness of the urinary stream, but he had no other complaints.

Past history: The patient had had gonorrhea some 22 years earlier. There was a history of mild exertional dyspnea with some palpitation for several years, but no other complaints.

Family history: The patient's father and two brothers had died of heart attacks.

Physical examination: Blood pressure was 208/118 mm. Hg; pulse was 92; temperature was 97°F. Aside from poor sphincter tone and a diffusely enlarged prostate, the physical findings were negative.

Laboratory findings: On admission, there was an elevated sedimentation rate of 46 and a blood urea nitrogen of 84 mg. per cent. The hemogram, fasting blood sugar, creatinine, and alkaline phosphatase levels were normal. Urinalysis revealed a trace of albumin, 20-23 red blood cells, and 1-3 white blood cells per high-power field. An occasional degenerated renal cell was noted. X-ray examination of the chest revealed a calcified Ghon complex in the left lung, a suggestion of rounding of the left ventricular border, and calcification of the aortic arch. The ECG revealed left heart strain with signs of progression.

Hospital course: On the second hospital day, a suprapubic prostatectomy and a vesicle diverticulectomy were performed. The postoperative course was uneventful; the blood urea nitrogen fell to normal levels, and repeat urinalysis revealed 4+ albuminuria and persistence of red and white cells in the sediment. Blood pressure remained at levels of 150-160/88-90 mm. Hg. Pathologic reports revealed glandular hyperplasia of the prostate and a pseudodiverticulum of the bladder. The patient was discharged on the sixteenth hospital day.

Second Admission.—The patient was readmitted to this hospital 4 years later, in May, 1955, with a 5- to 6-week history of constipation and difficulty in moving his bowels. There had been no melena, cramping, anorexia, or loss of weight at that time.

Physical examination: Blood pressure was 180/120 mm. Hg; pulse was 110. The left pupil was larger than the right. Both reacted normally to light. The lung fields were clear. The heart was slightly enlarged to the left. There were no murmurs, and the rate was rapid, at 110. The liver was enlarged 1 to 2 fingerbreadths below the right costal margin.

Laboratory findings: Hemogram, fasting blood sugar, and urinalysis were normal. Blood urea nitrogen was 22 mg. per cent. Stool examination was negative for ova and parasites. Benzidine

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From the Michael Reese Hospital, Chicago, Ill.
Received for publication Jan. 4, 1960.

tests of the stool were 3-4+; guaiac was negative. X-ray examinations of the upper and lower gastrointestinal tract were normal.

Hospital course: During this hospitalization there were no complaints, and the patient was placed on no medication. He was discharged after 8 days.

Third Admission.—The patient was admitted for the third time on Jan. 1, 1958, with a history of progressive congestive failure and intermittent lack of memory and disorientation. The history was difficult to obtain, and the admitting house staff noted that the patient was not cooperative. The family, however, related a history of chest pain, swelling of the ankles, and shortness of breath.

Physical examination: Blood pressure was 190/100 mm. Hg; pulse was 88; respirations were 20 per minute. The patient, although slightly dyspneic, was in no acute distress. There was venous distention of the neck veins in the recumbent position. The anteroposterior diameter of the chest was increased, and bilateral moist râles were heard at the bases, most marked on the left. Heart tones were distant. No murmurs were heard. The liver was enlarged 4 fingerbreadths and was non-tender. There was Grade I-II, pitting, pretibial edema bilaterally.

Laboratory findings: The initial urinalysis revealed albumin but no abnormal sediment. Hemoglobin was 17.5 Gm.; hematocrit was 52 per cent; serum sodium was 136 mEq. per liter; serum Cl, K, Ca, P, fasting blood sugar, and creatinine were normal. Blood urea nitrogen was 22 mEq. per cent. Venous pressure was 140 mm. H_2O, and Decholin circulation time was 40 sec. on admission. X-ray films of the chest revealed cardiomegaly, bilateral pleural effusion, and pulmonary vascular congestion. Heavy calcification of the transverse portion of the aortic arch was again noted. An ECG was abnormal, with a left bundle branch system block and occasional auricular premature beats.

Hospital course: Treatment consisted of salt restriction, digitoxin (0.1 mg. daily), reserpine (0.25 mg. daily), and Thiomerin. Venous pressure was repeated after 4 days and was 105 mm. H_2O, and the circulation time fell to 30 sec. The patient seemed to improve slightly and was ambulated with little difficulty, although x-ray examination, when repeated, revealed no appreciable change in the cardiomegaly and bilateral effusion. Repeat blood counts revealed persistent mild elevation in hemoglobin, with values of 16.5 Gm., and hematocrit of 50 per cent. Sedimentation rates were normal. A creatinine clearance study revealed values of 46 and 51 c.c. per minute. Serum chemistries, when repeated, were normal, except for a Cl of 91.5 mEq. per liter. Because the patient had improved clinically, he was discharged after 12 days. In addition to digitoxin and reserpine, Diuril had been started, in doses of 1 Gm. b.i.d.

Final Admission.—The patient did fairly well until Sept. 16, 1958, when he was readmitted for the last time because of marked dyspnea, orthopnea, and nocturnal dyspnea. He was found to have a supraventricular tachycardia on the afternoon of admission, with a rate of 140 beats per minute.

Physical examination: The patient was found to be acutely ill, with moderate dyspnea and orthopnea. The jugular veins were distended when the patient was in the sitting position, and he was cyanotic. Blood pressure was 150/108 mm. Hg; pulse was 140 (regular); respirations were 28 per minute. Moist râles were heard in the lower half of both lung fields. The heart was enlarged to the left of the mid-clavicular line, and a Grade 2 systolic murmur was present at the aortic area. The liver was enlarged 4 fingerbreadths below the costal margin and was tender. Femoral pulses were palpable bilaterally. There was 1+ sacral edema. The ECG revealed a supraventricular paroxysmal tachycardia, at a rate of 145, probably auricular flutter with 2:1 conduction. The left intraventricular block was still present.

Hospital course: Treatment on admission consisted of oxygen, salt restriction, digitoxin, and Diuril. He was given extra doses of Cedilanid intravenously, and Thiomerin by injection. He improved somewhat, and a repeat ECG, 24 hours later, revealed auricular fibrillation with a moderate ventricular response. Oxygen was given intermittently after 3 days, and quinidine sulfate was started on the morning of the fifth hospital day. However, quite suddenly during the afternoon of that day, the patient became cyanotic and had gasping respirations. Blood pressure was not obtainable, and peripheral pulses were absent. Beating of the chest wall and intracardiac adrenaline were of no use, and the patient was pronounced dead.

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DISCUSSION

DR. LEVIN: A chest film made in 1951, during the first admission, shows that everything is within normal limits, except for marked calcification of the transverse portion of the aortic arch. The film made during his third hospitalization, 2 days after admission, discloses some cardiac enlargement, but this is somewhat difficult to evaluate because the diaphragm is moderately elevated. There is marked right, and minimal left, pleural effusion. There is also some vascular congestion. The next, and last, film was made 4 days later, and there is no significant change other than somewhat less fluid in the right pleural space. The pulmonary vascular congestion is unchanged. I have not shown the films of the gastrointestinal examinations done in 1951, because they were negative, and upon review, I could find nothing significant.

DR. PICK: In Fig. 1, the three electrocardiographic records at the left show evolution of a pattern of left ventricular hypertrophy and strain between 1939 and 1951, with progression to an incomplete left bundle branch block in 1958. The two records at the right in Fig. 1 were obtained 7 and 5 days, respectively, before death. On September 17, the ventricular action is rapid and regular, and the ventricular complexes have maintained the features of an incomplete left bundle branch block. This establishes the presence of a supraventricular tachycardia. Its origin is not clear, since atrial deflections cannot be identified with certainty. However, the ventricular rate of 145 suggests the presence of atrial flutter with a 2:1 ventricular response. In the last record (9-19-58) the ventricular action is slower (average 90) and completely irregular; no P waves are seen, and shallow, rapid, and uneven undulations distort the base line. Clearly, atrial fibrillation is present (supporting the assumption of atrial flutter on September 17). In Lead I, there is a pair of bizarre beats, most likely ventricular premature systoles. The change in atrial rhythm, the configuration of the ST-T, and the ectopic ventricular beats can all be attributed to digitalis effects.

In summary, this appears to be the usual course of events seen in hypertensive arteriosclerotic heart disease. On the basis of the electrocardiographic evolution, one could venture to predict the following anatomic findings: (1) considerable left ventricular hypertrophy; (2) coronary arteriosclerosis of moderate degree; (3) diffuse myocardial fibrosis; (4) no large confluent infarction.

DR. GOLDEN: When I first looked superficially at the chart of this 84-year-old patient, the diagnosis appeared rather simple: hypertension and chronic congestive failure, with sudden death following a myocardial infarct. However, upon a more careful perusal of the record, including the notes of the nurses, it seems that there is more to this particular case than I have already indicated. I plan to discuss this case in three phases. The first phase pertains to the patient's life or medical history up to the time of the last admission to the hospital on Sept. 16, 1958. The second phase is more or less one of anticlimax and concerns the last 6 days of the patient's life. The final phase is difficult for me to time because there are two possibilities, one which took place over a period of 25 minutes and the other over a period of 75 minutes. My discussion will be directed mainly to an explanation of the mode of death rather than to the exact pathologic cardiac changes.

Of interest in the patient's family history is the fact that all male members, his father and two brothers, died of heart attacks. His mother lived to 93 years of age, and one sister died of some type of brain disease. He was a heavy smoker.

The first admission to this hospital took place in 1951, for a suprapubic prostatectomy and diverticulectomy of the bladder. The postoperative course was uneventful, and the patient was discharged on the sixteenth hospital day. At the time of the first admission for surgery, he had diastolic hypertension. The systolic pressure was 208, and the diastolic, 118 mm. Hg. Postoperatively, the blood pressure declined to 150-160 systolic and 88-90 mm. Hg diastolic. In 1955, during his second hospitalization, the pressure was 180 systolic and 120 mm. Hg diastolic, and in January, 1958, his pressure was still high, 190/100 mm. Hg. At the time of the final admission with chest pain in September, 1958, the systolic pressure was 150 and the diastolic, 100 mm. Hg.

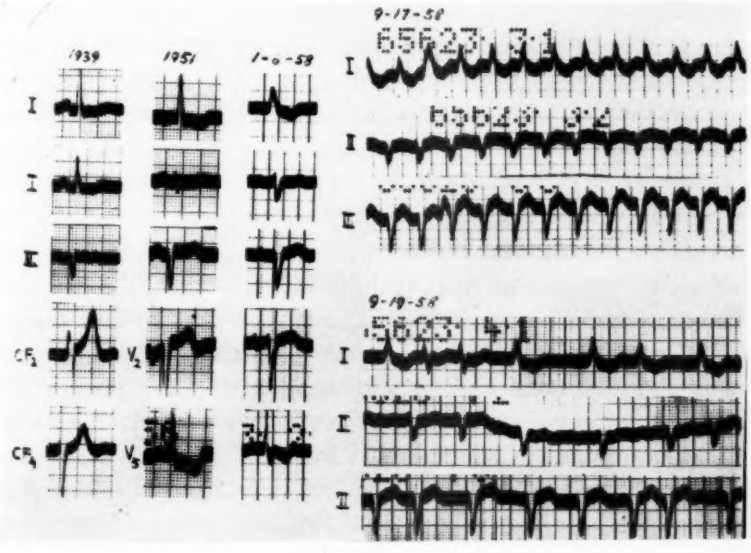

Fig. 1.—Series of electrocardiographic tracings.

In 1951, from the point of view of his cardiovascular system, the only symptoms that he had were mild exertional dyspnea and palpitation. These symptoms had been noted for several years. The heart was not enlarged, and there were no murmurs. The heart tones were slightly distant. An x-ray film of the chest showed rounding of the left ventricle and calcification of the aortic arch. His ECG showed left heart strain. He had had some electrocardiograms on file prior to 1951, and therefore the term "progressive" is included in the interpretation. In 1955, because of constipation, his gastrointestinal tract was investigated for an obstructive lesion. Radiologic findings were negative.

When he came to the hospital for the third time in February, 1958, congestive failure had progressed to a rather serious degree. There was a history of recent, more severe chest pain. The patient also had periods of disorientation and loss of memory, and the left pupil was described as being larger than the

right. The manifestations of congestive heart failure involved the pulmonary vascular bed and systemic venous system. The heart tones were distant, and there was significant emphysema. There was a systolic murmur at the apex, and the aortic second tone was accentuated. The liver was enlarged 4 finger-breadths below the costal arch and was non-tender. Grade II-III pretibial edema was present bilaterally. A film of the chest revealed cardiomegaly, bilateral pleural effusion, pulmonary vascular congestion, and heavy calcification of the transverse portion of the aortic arch. An ECG was abnormal, exhibiting left bundle branch system block and occasional auricular premature beats. At this time it was also observed that there had been an increase in hemoglobin and of the hematocrit, probably secondary to progressive pulmonary emphysema, peribronchial disease, and heart failure. The patient responded to the usual medication for congestive failure. Treatment consisted of salt restriction, digitoxin (0.1 mg. daily), reserpine (0.25 mg. daily), and Thiomerin.

Now we come to the second phase; and that began, as you recall, with the admission to the hospital for the last time, 6 days before death. He was admitted because he had become acutely ill, with marked dyspnea and orthopnea. Manifestations of more marked congestion of the pulmonary vascular system and the systemic venous system were present. The outstanding difference at this time was that he had a tachycardia with a ventricular rate of 140 beats per minute. The ECG revealed an auricular flutter with 2:1 auriculoventricular block and, also, intraventricular block.

Treatment consisted of oxygen, salt restriction, and Diuril. He was given Cedilanid (0.4 mg.) and Thiomerin (parenterally). He improved, and the ventricular rate diminished. The ECG at this time showed a change from flutter to fibrillation. During the next 3 days, he apparently did quite well and there isn't much in the progress notes to indicate anything that might be dramatic or unusual. However, I would like to read some of the notes in the nurse's chart on the final day. "He slept well the night before; he had eaten a rather good breakfast at 8:00 A.M. He slept from 9 to 11, and at noon his wife fed him his lunch."

The final phase probably began sometime in the morning, but the events after 1:00 P.M. were most significant. His physician had administered digitalis and had secured the results he desired. However, on the final day of the patient's life, in view of the fact that the abnormal rhythm was of short duration, it was considered worth while to try to convert the auricular fibrillation to normal sinus rhythm. To accomplish this, 3 grains of quinidine sulfate were prescribed. Before each subsequent dose, the patient was to be observed by a member of the house staff for evidence of dangerous side effects associated with the administration of the drug. The attending physician did something else; because the patient had not moved his bowels in 4 days, he ordered an enema.

I will take up the question of the enema first. The enema was administered at 1:50 P.M. The notes of the nurse simply state "enema by orderly." There is no mention of the results obtained. No mention is made of the length of time that he was on the bedpan. At 2:10 P.M. he was off the bedpan, and it was observed that his respiration became gasping in character and within 5 minutes had

ceased. The patient was pronounced dead. Had he sustained an infarct in the recent past or at the time of death? There is no evidence of a recent infarction in the electrocardiograms, but in the presence of left bundle branch system block, evidence of recent infarction is often not discernible. If one assumes that there had been a recent infarction, straining on the bedpan, after not having moved his bowels for 4 days, might have resulted in rupture of the ventricular wall.

The first dose of quinidine was administered at 1:00 P.M., and the patient died at 2:15 P.M. Was the sudden death due to a deleterious effect of quinidine? Within 1 hour and 15 minutes of an oral dose of the drug, the blood level may be at its maximum. In a hypertensive individual with severe myocardial disease previously treated with digitalis, fatal ventricular fibrillation may develop following the administration of quinidine.

In summary, it is my opinion that death was due to an untoward effect of quinidine in a hypertensive, aged individual with severe diffuse myocardial disease of vascular origin.

DR. RUBENSTONE: Dr. Golden has summarized the case very nicely from the standpoint of the terminal mechanism of death and has divided the patient's disease into three phases. At the very beginning of his discussion, Dr. Golden felt apparently that a differential diagnosis was unwarranted, in that, although many conditions could be included, the overwhelming one to be considered, and the one he so justifiably used from the practical point of view, was the one of advanced coronary arteriosclerosis with resultant myocardial disease.

This 84-year-old white man certainly did have advanced severe occlusive coronary artery atherosclerosis. The heart showed areas of interstitial fibrosis with a pattern characteristic of coronary artery disease. However, and particularly in a clinical-pathologic conference, the practical and commonplace is not always necessarily the diagnosis. As gathered from the clinical discussion, the pathology centered about the heart. Grossly, the heart weighed 650 grams and had a striking appearance. The right wall measured 6 mm. in thickness, and the left wall, 20 mm. The cross section of the heart muscle was the striking feature. The muscle was pale and homogeneous, with a distinct, firm, and waxy consistency. Otherwise, the heart valves were relatively normal, as was the pericardium. Hematoxylin and eosin stained sections of the heart revealed what appeared to be both a focal and diffuse massive replacement of the muscle fibers by homogeneous, relatively acellular tissue (Fig. 2). A battery of special stains revealed that the van Gieson mixture stained this material a yellow color rather than the ordinary bright red color of fibrous tissue. The crystal violet stain (Fig. 3) revealed a tremendous infiltration and replacement of the heart muscle by metachromatic-staining material characteristic of amyloid. Congo red stain showed only a slight pale red color. Silver stain for elastic reticulum[1] revealed a tremendous increase in the length and thickness of the reticulum fibers (Fig. 4) as compared to those found in the normal heart (Fig. 5). Amyloid was also deposited in the veins of the heart, but was not present in the arteries. As regards the rest of the organs, many showed some amyloid deposition confined to blood vessels. These deposits were particularly prominent in the spleen, lungs, thyroid, and gastrointestinal tract. It was interesting from the standpoint of etiology

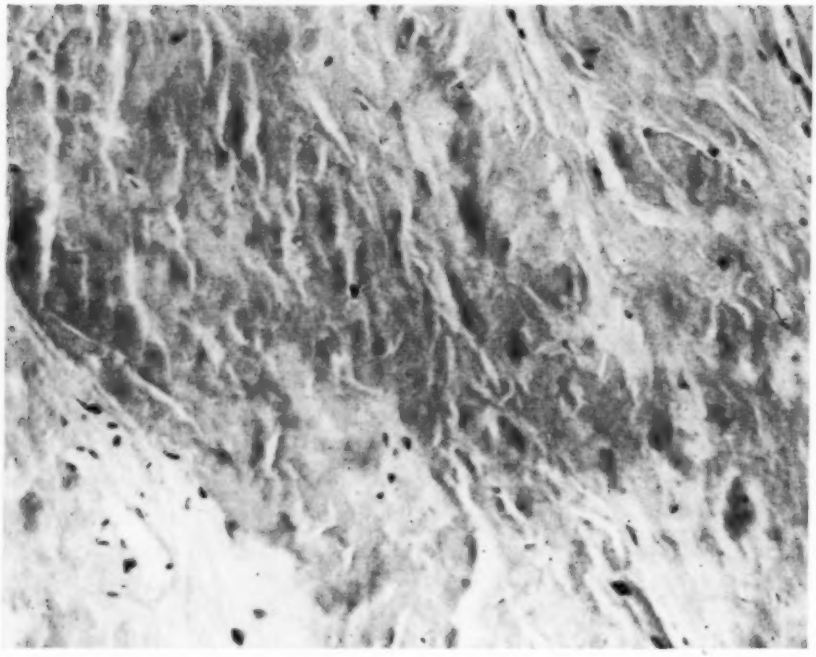

Fig. 2.—Hematoxylin and eosin stained section of heart showing massive replacement of the heart by amyloid (high-power magnification).

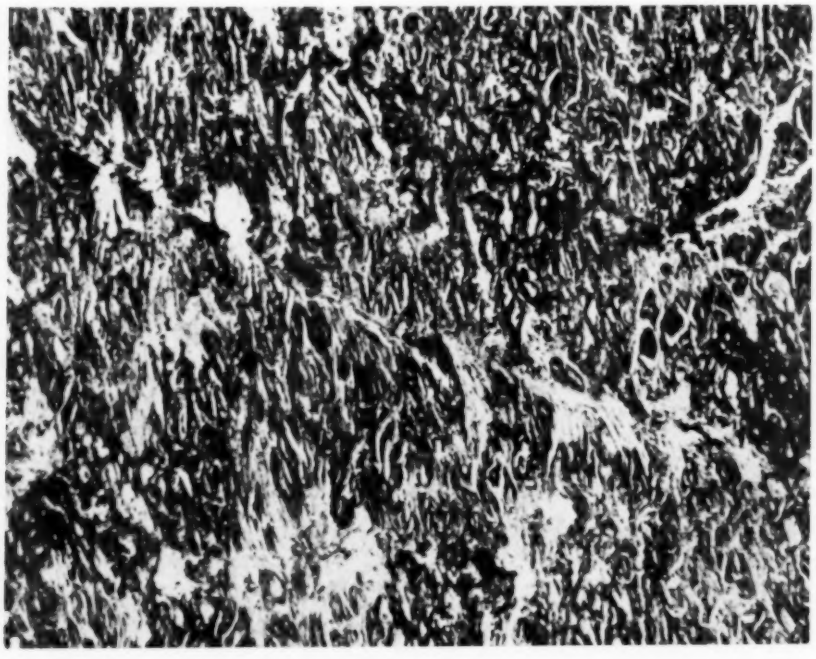

Fig. 3.—Crystal violet stained section of heart showing amyloid deposition (low-power magnification).

Fig. 4.—Silver stained section of heart showing marked increase of reticulum fibers (high-power magnification).

Fig. 5.—Silver stained section of normal control heart showing distribution of reticulum fibers (high-power magnification).

of senile amyloid of the heart that the seminal vesicles (Fig. 6) also showed evidence of amyloid deposition, which has been described by Bursell[2] to be related to age.

It was actually the purpose of this clinical-pathologic conference to demonstrate the entity of amyloidosis of the heart occurring in the aged. Even though this is a rare condition, it is important to present such rarities at clinical-pathologic conferences. Only by including rare conditions will we be able to correlate clinical findings with the pathologic findings. It is quite true that perhaps the diagnosis of amyloidosis could not be made from the clinical findings in our present knowledge in this case, but it is important to know whether or not such a diagnosis in the future could be entertained or at least be included in the differential diagnosis in retrospect. For example, can the symptoms of quinidine sensitivity be caused by amyloidosis of the heart?

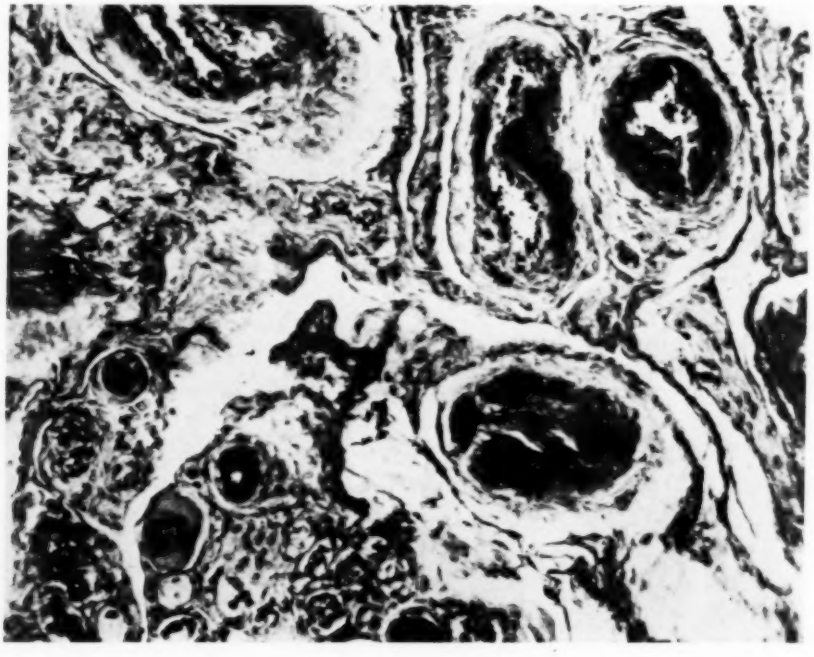

Fig. 6.—Hematoxylin and eosin stained section of heart of seminal vesicle showing amyloid deposition (high-power magnification).

Amyloid has been divided into four main categories, as follows: (1) secondary (typical), (2) primary (atypical), (3) localized amyloid tumors, and (4) amyloidosis associated with multiple myeloma. Senile amyloidosis of the heart is in the category of primary (atypical) amyloid, both in distribution and tinctorial qualities. It occurs from 1.5 to 13 per cent[3,4] of patients over the age of 70. Gross[1,4-14] and microscopic[1,5-18] descriptions of amyloid of the heart have been amply presented in the literature. Distribution may be mild and patchy, with involvement giving a "honey-combed" appearance to the heart fibers, or it may be massive, with complete obliteration of the architectural features

of the heart, as it was in the case presented in this report. Current theories as to the pathogenesis include, among others, malnutrition, senility, and derivation from degenerated elastic fibers.[1] Senile amyloid of the heart may be an incidental finding at autopsy or may represent a contributory or even direct cause of death.

I would like to conclude with Dr. Golden's analysis of the cause of death. The untoward effect of quinidine in this case cannot be substantiated by gross or microscopic pathologic changes, and must rest on clinical grounds alone. This is to be expected in the light of the rapidity of death following the administration of quinidine. There was no evidence of pulmonary embolism or fresh myocardial infarction.

Diagnosis: Senile amyloidosis of the heart

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Annotations

Pheochromocytoma in Pregnancy

During the past decade, occasional reports of pheochromocytoma complicating pregnancy have appeared in the obstetrical literature. Prior to 1949, but 5 cases were found by Bowen[2] in his survey, and at the present time somewhat less than 40 cases have been reported (Dean[4] found 32 in 1958, and added 1 case). Although this tumor is rare (8 cases in 1,700 patients undergoing surgery for hypertensive disease),[7] its occurrence in pregnancy is frequently catastrophic and is attended by 45 to 50 per cent maternal mortality despite a high curability rate if correctly diagnosed and surgically treated. As is frequently the case with other medical or surgical complications, the circumstance of pregnancy not infrequently delays or misdirects diagnostic efforts in favor of statistically more likely obstetrical problems. In the case of chromaffin tumors, the occurrence of hypertension, particularly in the latter half of pregnancy, suggests the diagnosis of acute toxemia (50 per cent of the cases reviewed by Dean), and during the puerperium the intervention of shock in these unfortunate patients suggests obstetrical causes of hypotension, especially vascular accidents, uterine rupture, or other hemorrhagic complications. Diagnostic confusion with acute toxemia of pregnancy has been pointed out by many authors,[2-4,6,12,14,16,17] and the confusion of "obstetric shock" in the puerperium with pheochromocytoma has also been noted.[2,13]

The first description of this tumor was that of Fränkel,[5] in 1886, but successful surgical removal was not performed until 1927, by Dr. Charles Mayo.[10] Apparently, the first reported case correctly diagnosed and surgically treated during pregnancy is that of Keir.[8] Adrenalectomy was performed on this patient during the third month and she was subsequently delivered at term of a normal infant. The difficulties in diagnosing pheochromocytoma during pregnancy or the puerperium is indicated by the fact that only 2 other reported cases have been correctly diagnosed in association with pregnancy.[4,9] Both patients were delivered by cesarean section. Adrenalectomy was performed on Dean's patient at delivery; Maloney's patient was operated upon on the seventh postpartum day.

Approximately 90 per cent of the chromaffin tumors are found in the adrenal glands, although they may develop at other sites of chromaffin-tissue distribution. Clinical features depend upon the relative amounts of epinephrine or norepinephrine secreted. According to Palmer and Castleman,[11] essentially two clinical pictures are seen: first, that characterized by profound shock, frequently developing after only slight trauma (these cases represent the majority of patients dying during the puerperium), and second, the paroxysmal syndrome associated with hypertension. The signs and symptoms are generally known and are well described by Smithwick and by Graham.[15] Unfortunately, the hypertension may be sustained rather than paroxysmal, and vasomotor symptoms may not be prominent or may be obscured by the myriad of complaints of pregnant women. Hypermetabolic phenomena may be absent. Clinical testing, too, by provocative or lytic techniques are not only attended by risk to the patient, but are not without error, and chemical determination of the metabolites of epinephrine and norepinephrine are tedious at best and in many areas not generally available to the clinician. Because of these circumstances, and in view of the probability of the occasional occurrence of pheochromocytoma in any large obstetrical experience, the medical consultant as well as the obstetrician must be alert to the

possibility of chromaffin tumors in situations in which hypertension complicates pregnancy. Although suspicion is essential to diagnosis, the basic problem in screening the hypertensive patient appears to be a chemical one. In this regard the newer techniques of isolation and determination of 3-methoxy-4-hydroxy-d-mandelic acid show promise in providing a reasonably accurate and technically feasible diagnostic tool for general usage.[1]

Richard L. Burt, Ph.D., M.D.
Winston-Salem, N. C.

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Autoantibodies

It has often been suggested in recent years that certain lesions of the heart, kidney, brain, and other organs may be caused by antibodies to the patient's own tissues. Such an autoimmune mechanism has been postulated in rheumatic fever, rheumatoid arthritis, acute nephritis, polyarteritis, systemic lupus erythematosus, multiple sclerosis, hemolytic anemia, and many other conditions. Although the body does not normally produce antibodies against its own components, it has been suggested that infection or drug allergy may alter the antigenic property of tissues and so provoke an autoantibody response. Also, it is possible that components of tissues which have had no contact with reticuloendothelial cells in fetal life may be treated as foreign antigens if released into the circulation later on.

The theory is speculative but fits a number of facts. Infection plays an important part in rheumatic fever and in acute nephritis, and drug allergy has been observed in certain hemolytic anemias and in the purpura that is caused by the drug Sedormid.[1,2] In animal experiments, also, the development of autoimmune nephritis or encephalitis appears to depend on the use of bacterial or other adjuvants to alter or enhance the antigenic properties of kidney or brain.[7,21,25]

Recently, the finding of autoantibodies to thyroglobulin in Hashimoto's thyroiditis (struma lymphomatosa) has given the stimulus to research along similar lines in a number of diseases of unknown etiology. The postcardiotomy syndrome and certain forms of myocarditis are being investigated from this point of view, and the presence of autoantibodies against various tissues has now been reported in rheumatic fever,[14] hepatitis, cirrhosis and systemic lupus,[11] Sjögren's syndrome,[13] orchitis,[8] nephritis and the nephrotic symdrome.[15-17] These results require confirmation, and even if autoantibodies are present, it may not follow that they are a cause of disease. Some of the pitfalls and difficulties of the subject are illustrated by the detailed work which has been recently carried out on disorders of the thyroid gland.

There have been several reasons for suspecting an autoantibody reaction in Hashimoto's disease. In 1953, Fromm[10] observed that the total globulins in the blood are raised, as they are in immune reactions and in some other conditions. The empirical liver-function tests give abnormal results, which is further evidence of globulin changes.[20] A progressive impairment of thyroid function often occurs, suggesting a continuing destructive process, and this appears to be reversed temporarily by steroids.[22] Histologically, there is infiltration of the thyroid with lymphoid tissue, lymphocytes, and numerous plasma cells; and in 1956, Rose and Witebsky[28] produced an almost identical reaction in rabbits by immunizing them against a mixture of rabbit thyroid extract and Freund's adjuvant. Finally, Roitt and Doniach[26] have shown that the serum of patients with Hashimoto's disease contains a precipitating antibody that reacts with an extract of human thyroid.

The use of different techniques for detecting antibodies has given somewhat conflicting results, but it is now clear that at least two distinct antibodies may be present in a number of different thyroid disorders. One antibody reacts with thyroglobulin and is demonstrated by the precipitin reaction, by tanned red cell agglutination,[24] and by skin anaphylaxis in the guinea pig.[23] A second antibody reacts with a constituent of thyrotoxic thyroid tissue and is demonstrated only by the complement-fixation test. The results of fractionation studies have led Belyavin and Trotter[5] to suggest that the antigen concerned is intracellular and that it contains no thyroglobulin and very little iodine. Recently, Anderson and his colleagues[4] have suggested that a third type of antibody is sometimes present, which reacts with thyroglobulin and also fixes complement.

What was once so clear has thus become rather confused. Roitt and Doniach[27] can now detect antibodies in 98 per cent of the patients with Hashimoto's disease, but also in 83 per cent of the adult patients with spontaneous myxedema, 64 per cent of the thyrotoxic patients, 33 per cent of those with nontoxic colloid goiter, 68 per cent of those with subacute thyroiditis, and 29 per cent of the patients with thyroid cancer. It is of interest that the highest antibody levels are found in Hashimoto's disease and in spontaneous myxedema, which are the only two of the above-mentioned conditions in which antibodies have so far been detected by Ovary's guinea-pig test. Apart from the theoretical interest of this finding, the simple guinea-pig technique may therefore have considerable clinical value as a diagnostic test.

A few patients with Hashimoto's disease have cirrhosis,[20] Paget's disease,[18] nephrosis,[19] or Sjögren's disease.[12] Except for Paget's disease, these are all conditions in which the presence of autoantibodies has recently been reported. Patients with Hashimoto's thyroiditis may also have Addison's disease, and Anderson and associates[3] detected antibodies against both the thyroid and the adrenal in such a case. This raises the question whether these patients may have a generalized disturbance of the immune mechanism. In keeping with this is Roitt and Doniach's finding that in a few cases of Hashimoto's disease, complement-fixation reactions can be obtained with extracts of several different human organs. This has been confirmed by Anderson, who notes that if these reactions are of an immunologic nature, they represent another feature of the abnormal immunologic status of these patients.

It is difficult to interpret these findings. If autoantibodies are merely a by-product of tissue injury and have nothing to do with the cause of disease, what is the explanation of Rose and Witebsky's experimental thyroiditis in rabbits? Why is this caused by injecting thyroid and Freund's adjuvant, and why is it associated with the presence of autoantibodies in the serum? On the other hand, if autoantibodies can injure the thyroid cells, why is there not more evidence of a cytotoxic effect in patients with thyrotoxicosis who have antibodies in the blood? When Roitt

and Doniach injected monkeys with serum from patients with Hashimoto's disease, why was there no damage to the thyroid gland of these animals, in spite of a good cross-reaction in vitro between this serum and monkey thyroid?

One thing seems plain: that antibodies may be found when any nonspecific disturbance has affected the normal structure of the thyroid gland. In these circumstances their presence would appear to be a secondary phenomenon. It is not known whether these circulating antibodies have any cytotoxic effect, or whether they provide any indication that antibodies have become bound in the tissues. An analogous situation may be present in allergic encephalitis, and although an autoimmune mechanism seems most probable in this condition, there is no correlation between the level of antibodies in the blood and the presence of lesions in the nervous system. If circulating antibodies can cause cell destruction, this destruction must be of a limited nature in most thyroid disorders, or, as Blizzard and his associates[6] have suggested, might even be beneficial in disorders such as hyperthyroidism.

A different situation seems to be present in Hashimoto's disease and in some cases of spontaneous myxedema. Here there are striking lymphadenoid changes in the thyroid gland, remarkably high levels of circulating autoantibodies, and possibly a qualitative difference from other thyroid disorders in the response to the guinea-pig antibody test. In many patients with Hashimoto's disease there is also a suggestion of immune reactions involving several other tissues. On the available evidence it seems possible that an overactive immune response in these subjects allows a vicious cycle of potent antibody production and continuing cell damage to follow a minor disturbance of the thyroid and lead, in turn, to lymphoid infiltration, goiter formation, and, finally, destruction of the gland.

Autoantibodies might be expected to occur in two circumstances, one in which they play a major role in causing disease, the other in which they develop as a purely secondary phenomenon after a tissue has been injured. So far it is not known whether the autoantibodies that have been reported in human diseases fall into the first or the second category.

Maurice H. Lessof, M.D., M.R.C.P.
Samuel P. Asper, Jr., M.D.
Baltimore, Md.

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Responses of Resistance Blood Vessels to Increases in Transmural Pressure

The response to change in transmural pressure of the blood vessels chiefly responsible for the peripheral resistance to blood flow is of importance in at least two ways. First, the vessels are exposed to an increased transmural pressure in arterial hypertension, and an altered reactivity to the exposure might contribute to, or determine the course of, the hypertension. Secondly, local vascular reactivity may help to protect the circulation against the effects of gravity.

Passive vessels are distended by an increase in transmural pressure. If there is an active response,[1,2] the distention may be lessened, prevented, or reversed. An active response which only lessens distention is hard to detect while the pressure is raised, unless there is a perfectly passive vessel, perhaps provided by poisoning, available for comparison. If the pressure is suddenly removed, a persistence of the contractile force in the wall of the vessels may lead to a temporary narrowing of the vessels to less than their normal diameter.

Some recent animal experiments have indicated a narrowing of resistance vessels with increase in transmural pressure[3,4]; other experiments have indicated a distention.[5-8]

In the human forearm and calf the blood flow is reduced, and the resistance vessels are narrowed, following a period in which the transmural pressure is raised by venous congestion[9] or local exposure to subatmospheric pressure.[10,11] Similarly, if during arrest of the circulation to a limb the intravascular pressure is maintained at a higher value than usual, on release of the circulation the reactive hyperemia is less than usual.

The effectiveness with which the contractile response opposes the raised transmural pressure is variable. Slight venous congestion, of about 15 to 20 mm. Hg, causes no reduction in the rate of inflow of blood to the forearm or calf.[12,13] Since the perfusion pressure is reduced, the resistance vessels must be slightly distended. Higher venous pressures have been variously reported to cause a decrease[14] or an increase[15-18] in resistance, but venous-occlusion plethysmography is of doubtful

reliability as a measure of blood flow, and therefore of resistance, when the venous pressure is greatly raised; it may underestimate flow and therefore indicate too high a resistance. Calorimetric observations are believed to be more reliable under these conditions, and have indicated that venous congestion in the digits either reduces resistance[19] or leaves it almost unchanged.[20,21] Lowering the limb to the passive dependent position, which increases arterial and venous pressures about equally, diminishes resistance in the digits,[21,22] but greater increases in transmural pressure, brought about by local exposure to pressures which are 50 to 150 mm. Hg below atmospheric, increase resistance in the hand and toes.[23,24]

These calorimetric observations are supported by others in which blood flow and resistance have been inferred from measurements of the oxygen saturation of venous blood. In the dependent limb the vessels are slightly dilated,[25,26] but when the transmural pressure is raised to a higher value by local exposure to subatmospheric pressure, the vessels, which at first are distended, gradually return toward or beyond their initial diameter.[27]

As a whole, the evidence indicates that small increases in transmural pressure cause distention, there being insufficient evidence to say whether there is no response or merely an ineffective response. Moderate increases in transmural pressure elicit a response which sometimes leads to narrowing of the vessels. Severe increases cause the vessels to widen, perhaps by overcoming the contractile response.[23]

The response may be a myogenic one in the resistance vessels,[1,2,9] or it may depend on a detector in some other vessel linked to the resistance vessel by a nervous or humoral pathway,[15] or both mechanisms may operate. It is difficult, on the available evidence, to distinguish clearly between these possibilities, because transmural pressure cannot be changed in one type of vessel without inducing consequential changes in others. It does seem, however, that if the resistance vessels react to a raised pressure in the vessels, the reaction must be very weak.[13,19,20]

All of the observations so far mentioned are acute ones. The most clear-cut evidence about persistently raised transmural pressure comes from the observations[28] of cases of coarctation of the aorta. The pressure is greater in the arms than in the legs, and so also is the resistance, so that the rate of blood flow is normal in all limbs. It seems most probable that the altered resistance in the limb is a consequence of the altered pressure, but the mechanism of the change is not known.

A. David M. Greenfield, D.Sc., M.B.
Belfast, Northern Ireland

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The Keys Equation

Dr. Ancel Keys and his colleagues have recently published a formula by which the responses in serum cholesterol to changes in diet can be predicted. The reliability of the formula was tested employing glycerides of saturated, monoenoic, and polyenoic fatty acids.[1]

A few years ago it was suggested by others that the ingestion of unsaturated fatty acids decreased the concentration of cholesterol in the serum, and that an inadequate intake of these acids might be the cause of the high serum cholesterols found so frequently in the Western civilization. It rapidly became apparent that (1) the degree of saturation or of unsaturation of the ingested fatty acids, (2) the types of fatty acids ingested, (3) the total fat consumed in the diet, (4) the effect of substitution or supplementation of the diet with various fatty acid components, (5) the effects of various factors in the oil derivatives other than the fatty acids (i.e., factors in the nonglyceride portion of the ingested fats) such as beta-sitosterol were of importance.

By the careful control of certain variables it was possible for Dr. Keys to formulate a prediction equation which is said to be capable of predicting the expected serum cholesterol change which would occur when certain dietary factors are altered. This equation is:

$$\text{Chol.}_2 - \text{Chol.}_1 = b\,(S_2 - S_1) + c\,(M_2 - M_1) + d\,(P_2 - P_1)$$

In this equation, cholesterol is in milligrams per cent; S, M, and P are, respectively, the percentage of the total calories in the diet supplied by glycerides of saturated, monoenoic, and polyenoic fatty acids; and the subscripts refer to the first and second diets. The coefficients b, c, d, in the equation are obtained by the method of least squares from the data of sixty sets of comparisons and turn out to be: $b = 2.68 \pm 0.08$, $c = 0$, and $d = -1.23 \pm 0.07$. These coefficients apply to the

average change in cholesterol of men who have an average of about 225 mg. of cholesterol per 100 ml. of serum on a diet in which the values of S and P, as percentage of total calories, are about 20 and 3, respectively. Men who are intrinsically hypercholesteremic exhibit greater cholesterol response to dietetic changes, whereas hypocholesteremic men are less responsive than the reference men.

Keys' group stated that, in man, (1) oleic acid glyceride in the diet is substantially the equivalent, in serum cholesterol effect, of equal calories from carbohydrate, (2) the glycerides of saturated fatty acids in ordinary fats raise the serum cholesterol level, (3) the glycerides of polyunsaturated fatty acids (mainly linoleic acid) lower serum cholesterol, (4) intrinsic relative hypercholesteremia is generally associated with relative hyperresponsiveness to dietary fat changes, and (5) these relationships allow reasonably accurate predictions of group average responses in serum cholesterol level to given changes in dietary fats.

This formula points out the significant role played by the glycerides of fatty acids (stearic and palmitic mainly) and the glycerides of the polyunsaturated fatty acids (linoleic acid mainly) in the diet. The formula does not take into consideration nondietetic factors such as stress and endocrine activity.

Harold L. Karpman, M.D.
Los Angeles, Calif.

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The Elusive Ductus

Uncomplicated patent ductus arteriosus (PDA) is the most easily recognized congenital cardiac defect at the bedside. On the other hand, when associated with pulmonary hypertension or with other congenital heart lesions the usual clinical features of PDA can be so altered that it may be totally unrecognized unless complex diagnostic studies are utilized to clarify the situation. When PDA is unrecognized, there may be tragic consequences. First, when PDA is allowed to continue, a stage of pulmonary hypertension may be reached which prohibits surgical correction of a defect that previously could have been completely corrected. And secondly, undiagnosed PDA may enormously complicate and increase the risk of open-heart surgery for the correction of some associated defect.

Although PDA may coexist with many other congenital or acquired heart lesions, the defect which most frequently causes confusion in diagnosis is a ventricular septal defect (VSD). These disorders, separately or together, can present a similar developmental history, and subsequently can be associated with pulmonary hypertension persisting from infancy; or progressive lesser circulation pressure and resistance can gradually appear in later life. As pulmonary pressure rises, physical signs and murmurs are likely to be drastically altered. Whereas the early stages are characterized by left-to-right shunts and either left heart or mixed left and right heart dynamic characteristics, the right heart is increasingly burdened as pulmonary pressure rises, so that the shunt equalizes, disappears, or even reverses. The classic machinery type of murmur of PDA may be altered so as to occupy only systole; at another stage it may totally disappear, and occasionally be replaced by the murmur of pulmonic valve incompetence. The usual systolic murmur of VSD may similarly disappear or be followed by the murmur of pulmonic insufficiency. The lesions at this stage, whether separate or combined, are associated with arterial unsaturation on exercise, and eventually at rest, and the classic lower extremity cyanosis of reversed ductus may become generalized. The ECG, as would be expected, varies widely, showing left, right, or mixed preponderance. Persistence of left ventricular preponderance probably favors PDA. Roentgen study is usually of little help in distinguishing the two. Right heart catheterization in the presence of pulmonic incompetence will show an increased oxygen saturation of blood from the right ventricle in either case, and in many instances a further increment in oxygen content in blood from the

pulmonary artery might not be detected. Some patients, diagnosed as having VSD, have been explored for open-heart repair, and PDA was found, sometimes only after the heart had been opened. The experienced cardiac surgeon now knows that a silent PDA may masquerade as a VSD, and that VSD may also be combined with unsuspected PDA. For this reason, the region of the ductus is carefully examined before preparing to use the pump-oxygenator. Correct diagnosis can usually be made preoperatively by aortography or appropriate indicator dilution technique.

Additional diagnostic confusion occasionally occurs when VSD coexists with aortic insufficiency, for a double murmur will be present which closely mimics the murmur of PDA.

Although bedside diagnosis will continue to suffice for the recognition of most congenital cardiac lesions, the complex described here should always be suspected in the patient with severe pulmonary hypertension so that the special techniques that have been discussed may be utilized to prevent serious errors in diagnosis, and possible disastrous consequences.

Frank W. Davis, Jr., M.D.
Baltimore, Md.

Book Reviews

ADVANCES IN CARDIOLOGY. II. Edited by Prof. Dr. R. Hegglin and E. Luthy, Zurich, Switzerland. Basel and New York, 1959, S. Karger, 337 pages, 139 illustrations. Price: 59 sFr.

This book is a collection of 27 selected lectures from the Third World Congress of Cardiology held in Brussels, Belgium, September, 1958. The lectures are grouped in four major categories: (A) Congenital and Acquired Heart Disease (all surgical in scope); (B) Cardiac Failure (subdivided into Hemodynamic and Metabolic Problems); (C) Diseases of Coronary Vessels; and (D) Correlations Between Lung and Heart.

For those who did not attend the Congress or who have not had the abstracts available to them, this collection of lectures will give an idea of the type of papers presented. The book contains little if any new information inasmuch as the lectures selected are, for the most part, of a review nature. In fact, nearly all give credits for having been published elsewhere, and one goes so far as to dismiss the bibliography with one reference to a previously published article in which the complete bibliography may be found.

Prof. Dr. Hegglin, a cardiologist, has selected lectures in a manner which will permit some readers to enjoy the facility of neatly packaged reviews, but many of those interested in the subjects covered are probably familiar with or have access to papers and texts by the authors in the British and American medical literature (16 of the 27 lectures). Unfortunately, 7 of the remaining 11 are printed in French, with only an English summary. Ironically, although the title of the book is in three languages, German, English, and French, the articles in English have no foreign language summary, and except for the group headings, no German appears elsewhere in the book. The collection could have been of more value if the papers given in English had been published in French with an English summary and bibliography, and if those given in French had been published in English.

MITRAL VALVULOTOMY. By Harold J. Stewart, M.D., Professor of Clinical Medicine, Cornell University Medical College, New York, Attending Physician, The New York Hospital; and Frank Glenn, M.D., Lewis Atterbury Stimson Professor of Surgery (Chrm.), Cornell University Medical College, New York. With the assistance of George Lovell, M.D., Carl Wierum, M.D., and Robert A. Keisman, M.D. Springfield, Ill., 1959, Charles C Thomas, Publisher, 218 pages, 63 illustrations. Price $10.50.

This book documents the authors' clinical observations on 300 persons with mitral valvulotomies, and records their conclusions derived therefrom. One author is a cardiologist with clinical and investigative experience, and the other is an eminent surgeon. The observations are, therefore, beyond question. Nevertheless, it is important to determine whether the observations justify the conclusions. Indeed, this type of book should serve as an introductory lesson in a course in a multidiscipline composed of biostatistics, logic, and psychology, for motivation does enter into a physician's operational reasoning.

Patients with predominant mitral stenosis and dyspnea were accepted for surgery. Predominant mitral stenosis was based upon clinical judgment because technical procedures did not decrease their errors.

Slightly more than half the patients operated upon in 1951 were dead in 1956. Slightly less than one quarter of all patients were dead within less than three years of operation. The reviewer thinks that such a mortality is not justified unless evidence is presented that nonsurgical treatment in such a group is apt to have at least as high a mortality. Such evidence is not presented. On the contrary, dyspnea without (right) heart failure, a clinical status compatible with many years of life, was the predominant indication for operation. Furthermore, the authors do an elective cholecystectomy before valvulotomy, an illogical practice, in the reviewer's opinion, and one which hardly suggests a sick cardiac patient. Incidentally, the reviewer counted 21, not 20, late deaths.

The case for prophylaxis against emboli and infarction is tilted in favor of surgery by the simple expedient of omitting those accidents which occur at operation or soon thereafter. Actually, the natural recurrence rate as a basis for comparison is not discussed.

Only 32 of 300 roentgenograms were available for comparison postoperatively, and of these the majority showed larger silhouettes. Only one electrocardiogram is briefly described.

Although the mortality rate for the second 200 cases is double that of the first, the results of the second group are regarded as better than those of the first because improvement occurred in 79.4 per cent of the second as compared to 72 per cent of the first. The statistical significance of these figures is not tested. Actually, the magic figure of 70 per cent improvement is maintained no matter how many die, by the simple expedient of referring only to survivors.

The authors conclude that the mortality rate in the long-term follow-up cannot be predicted from the short-term evaluation or from the inadequacy of the split as estimated by the surgeon at the time of operation. Is this not true because their patients were not anatomically homogeneous, because similar cardiac symptoms do not spell similar anatomic faults, and because rheumatic heart disease is more than a mechanical problem? Because splits are not always good, the authors anticipate a trend, as do all students of the subject, toward open-heart surgery.

COMPENDIO DI ELECTROCARDIOGRAFIA. By Vincenzo Masini, Rome, Il Pensiero Scientifico, 474 pages, 327 illustrations. Price: 4,500 lire.

This monograph is a manual for students of electrocardiography. It is clearly written and is based on typical documents. Even though there is no new contribution or new type of presentation, the book can be recommended to medical students for whom it is clearly intended.

THE SURGEON AND THE CHILD. By Willis J. Potts, M.D., Surgeon-in-Chief, Children's Memorial Hospital, and Professor of Pediatric Surgery, Northwestern University Medical School, Chicago, Ill. Philadelphia, 1959, W. B. Saunders Company, 225 pages. Price $7.50.

In view of the number of excellent, comprehensive books on pediatric surgery recently published, only an intrepid and insensitive author would approach the task of a new book on this subject without considerable misgivings. Dr. Potts could have spared himself any qualms that might have beset him in this regard, because his book, in the reviewer's opinion, serves a valuable purpose and undoubtedly will occupy the place left vacant by the obsolescence of Ladd and Gross' monograph.

The Surgeon and the Child possesses the priceless ingredients of simplicity and brevity—two disciplines not easily attained when the complexity of some of the subjects, such as that of congenital heart lesions, is considered, and when one appreciates the temptation to expound which must come to a surgeon of Dr. Potts' wide experience. The monographic proportions of the book have been maintained by reducing the material to essentials, and yet such is the ability of the author as lecturer and teacher that none of the essentials in any given subject seems to be omitted. This is accomplished, as Dr. Potts freely confesses in the preface, by focusing "often in a somewhat dictatorial fashion." His sparkling sense of humor, however, makes it a pleasant dictatorship, with no trace of stuffiness or pedagogy. No one with this superb sense of humor can take himself completely seriously, and it is often obvious that the finger that is being paternally wagged is one that has previously been burned in the school of experience.

The chapter, "Preoperative Care," contains many diagnostic "pearls" known perhaps to many pediatricians but likely to be unfamiliar to the surgeon. Packed in close sequence, they are reminiscent of Mowgli's education in the Laws of the Jungle by Baloo but are no less valuable for the litany. The basic requirements of fluid and electrolytes in children are simply and concisely given. In regard to the use of milliequivalents for calculation, instead of the outmoded milligrams, one is amused but perhaps not surprised by the suggestion that "If the attending surgeon completed his training more than twenty years ago and has not concentrated on milliequivalents, it is often good judgment for him to look wise and say little as his resident calculates the electrolyte needs of the child."

Simplicity is the keynote of the chapter on anesthesia; prevention, that of the one on cardiac arrest. The tables of dosage for preoperative medication in the former chapter are worthy of preservation on pediatric wards not already so supplied.

The chapter on respiratory problems of the newborn, infants, and children is particularly interesting. The discussion of differential diagnosis in the newborn with respiratory difficulty and the manner of obtaining adequate roentgenograms is informative and valuable. It is in the chapters on congenital heart disease that Dr. Potts has shown an extraordinary capacity to distill the essence of the subject and present clearly the cardinal features of diagnosis and treatment. This is no mean feat in a field in which methods are legion, opinions often divergent, and techniques frequently complicated, and no doubt special interest in the field and wide experience have endowed Dr. Potts with this ability to crystallize the subjects. These chapters should serve admirably for a starting point for residents, for physicians who are not practicing pediatric surgery but who want to "keep up," or for those who want to have a point of departure for more detailed study. No one knows better than Dr. Potts that in this rapidly expanding and ever-changing field the last word has not been spoken. His comment on the eventual replacement of shunt operations, a field in which he so brilliantly pioneered, by open-heart operations is typical: "It has always been true that a father loves and favors his own child even though the child is definitely retarded. In self-defense and in defense of Smith, Blalock, Taussig and Brock, I am sure I may say that we are not grieving as the incomplete operations for tetralogy of Fallot are being laid aside for an operation which will cure and be relatively safe. As future surgeons pass the markers of these operations all we ask is that they say a few kind words." It is also typical of Dr. Potts that credit is given the younger members of the surgical team throughout these chapters.

In the chapter, "Congenital Atresia of the Bile Ducts," the section on diagnosis is excellent, but the results of surgical procedures corroborate other pessimistic reports in this field that seldom are anatomic structures suitable for a feasible shunt to relieve the biliary obstruction.

Dr. Potts' contributions in the field of gastrointestinal obstruction in the newborn and in infants are well known. His homespun emphasis on knowing whether the child has "vomited green" typifies his means of stressing early diagnosis and proper treatment. The reader will find innumerable, valuable, diagnostic and therapeutic suggestions based on wide experience with pyloric obstruction, malrotation of the bowel, meconium ileus, intussusception, and atresia and stenosis of the intestine. The chapter, "Congenital Atresia of the Rectum and Associated Defects," is particularly well written and deserving of the emphasis that Dr. Potts has given it, because as he concluded, "In general, atresia of the rectum is more poorly handled than any other congenital anomaly of the newborn. A properly functioning rectum is an unappreciated gift of greatest price." His plea is for proper management at the *first* operation for the malformed rectum.

The reader will, in all probability, find the opening chapters the most interesting, because in three beautifully written essays Dr. Potts reveals his philosophy of pediatric surgery, and, inadvertently, his deep understanding and love of children. He is outspoken in his belief that pediatric surgery is a specialty entitled to its place in the sun and prophesies that it will soon be so accepted. He also takes the opportunity to make a plea for more children's hospitals as complete, self-sufficient units.

The discussion of "The Deformed Child" delves into a philosophical problem to which there is no ready answer. To say that Dr. Potts comes up with "to each his own philosophy" would be an oversimplification of the matter. He discusses the impact on the family, the economic tangle which is often evolved, and the religious aspects of the problem. Naturally, he can give no absolute rules of conduct, but every physician can find guidance and comfort in this chapter should he be confronted by one of these unfortunates where "compassion wrestles with duty."

"The Heart of a Child" is a gem of medical writing which first appeared in the *Journal of the American Medical Association*, June 9, 1956, and which is fittingly reprinted in this book. The subject is considered from the point of view of the "philosophical" and not the physiological heart of a child. Dr. Potts' profound understanding and great love of children is clearly revealed without maudlin sentiment. The subject is most timely, because, undoubtedly, the emotional trauma unknowingly inflicted on children by hospitalization and operation is far greater and more frequent than is commonly suspected.

The format of the book is attractive and the print and quality of the paper are excellent. Subjects are well organized and the index seems adequate. The absence of legends for some of the illustrations is surprising. When the chapters are read in continuity, this absence is not conspicuous, but with use of the book for spot reference the omission could prove somewhat irksome.

Without doubt, in the reviewer's opinion, this is the most readable medical book to be published in many years. Nowhere else can one find in so short a space and with so little effort sugar-coated "pearls," a touch of Mark Twain, literary style reminiscent of Moynihan, and a glimpse of the *Heart of a Surgeon*.

DIAGNOSIS OF CONGENITAL HEART DISEASE. By Sven R. Kjellberg, Edgar Mannheimer, Ulf Rudhe, and Bengt Jonsson, Karolinska Sjukhuset, Stockholm, Sweden. Second edition, Chicago, 1958, The Year Book Publishers, Inc., 866 pages. Price $28.00.

This is the second edition of a book which already has achieved an important place in the cardiological literature. The clinical case material which formed the foundation of the first edition has been almost doubled in the present issue. The major key to this book's usefulness is its presentation of the extensive personal experiences of its authors, who are all members of the Pediatric Clinic of Karolinska Sjukhuset, Stockholm. The bibliography consists of 727 selected references which serve to verify and amplify this broad basis of personal experience.

The 742 cases of congenital heart disease presented in this edition have been selectively explored and analyzed from the standpoint of clinical features, phonocardiography, electrocardiography, roentgenography, fluoroscopy, electrokymography, and right- and left-sided angiocardiography and cardiac catheterization. Procedures of more recent value, such as indicator-dilution dye techniques, radioactive krypton methods, vectorcardiography, and intracardiac phonocardiography and electrocardiography, have not been covered. A few of the rare types of congenital heart lesions are not included. These omissions, however, do not greatly detract from the value of this volume. It represents an extraordinary repository of factual material concerning the cases investigated. Each author has written the sections dealing with his own speciality. The volume is well indexed and profusely illustrated. Angiocardiography occupies a major portion of the presentation, and the illustrative reproductions are of excellent quality. Electrocardiograms are surprisingly few in number. The over-all orientation of this book is toward embryology, pathology, physiology, and diagnostic methods; treatment is hardly mentioned.

The majority of cardiologists will find this volume useful as a reference work and, as such, it can be highly recommended.

Letters to the Editor

Monongahela Bldg.
Morgantown, W. Va.
December 16, 1959

To the Editor:

Dr. Don Fisher fails to extract the real flavor, and misses the valuable stimulus of Michael Korns' paper on pericardial effusion. Dr. Fisher is too young, I expect, to have had a chance to watch the real art of physical examination. I myself had, in reading this paper, the great pleasure of renewing my youth, when among my teachers (and an expert in physical diagnosis) was Dr. Horace Korns, onetime Editor of the *American Heart Journal*, whose fine guiding hand can be detected in his son's enjoyable paper.

It is not a bad thing to be reminded that these physical signs exist, so that one will again take pains and search for them. They are not always there, of course, but they are not founded in fancy. Many skilled observers in the past, not just the famous ones in the bibliography, found them useful, and we should be using them today. What's the alternative?—"Let's look at the x-ray." "What's the lab report?" And what do they tell you, half the time?—Confusion! Even though physical signs may at times lack specificity and sensitivity, there is an art in their employment, and value to be gained from them. All too often, laboratory tests, even if available, are fully as fallible as the examiner's senses.

To me, the big value in Mr. Korns' paper was its stimulus to take more pains—returning to the good practices I was taught, so many of which in this "Scientific" Era have gone by the board.

F. R. Whittlesey, M.D.

1150 Fifth Avenue
New York, N.Y.
December 20, 1959

To the Editor:

In a letter to the Editor (*American Heart Journal* 58:939, December 1959) Dr. Don L. Fisher refers to an article by M. E. Korns, "Bedside Diagnosis of Pericardial Effusion," in which more extensive use of physical diagnosis is advocated.

Dr. Fisher points out that physical signs for the detection of pericardial effusion lack specificity and sensitivity. Hence, there is a great need for laboratory signs. To prove the usefulness and diagnostic value of physical signs, an objective analysis of the latter in a series of patients, and comparison with laboratory tests would be required, according to Dr. Fisher.

I happen to have just finished a study in which diagnostic results obtained by percussion in a series of 32 proved cases of pericardial effusion were compared with the results of x-ray study.

The diagnostic accuracy based on percusion was more than four times higher than that of x-ray examination. Roentgenologic study, because of its inadequacy in differentiating between cardiac dilatation and pericardial effusion, is notoriously unreliable in the diagnosis of pericardial effusion (Lancet 2, July 4, 1955, p. 25, Editorial).

WILLIAM DRESSLER, M.D.

ALLEGHENY GENERAL HOSPITAL
PITTSBURGH PA.
DECEMBER 30, 1959

To the Editor:

I love a good physical sign as much as anyone; but my clinical experience leads me to contradict the validity of Auenbrugger's sign of pericardial effusion, as it is translated and attributed to him by Korns. Therefore, I ask for some confirmatory evidence. This should not include general praise of the art of physical diagnosis, a comparison of ages (Dr. Whittlesey's 58 versus my 41), or the citation of ancestral lineage. In regard to use of the sign by "skilled observers in the past," the bibliography has given no such supporting reference. Let us honor the successful achievements of Auenbrugger, not resurrect his mistakes.

DON L. FISHER, M.D.
Director,
Cardio-Pulmonary Laboratory